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- (71) **Applicant:** THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US).
- (72) **Inventor:** FISHMAN, Mark, C.; 43 Kenwood Avenue, Newton Center, MA 02459 (US).
- (74) **Agent:** ELBING, Karen, L.; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).
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**WO 01/51666 A1**

(54) **Title:** METHODS FOR DIAGNOSING AND TREATING HEART DISEASE

(57) **Abstract:** The invention provides methods of diagnosing heart disease, such as heart failure, screening methods for identifying compounds that can be used to treat or to prevent heart disease, and methods of using these compounds to treat or to prevent heart disease. The invention also provides animal model systems for carrying out the screening methods.

## METHODS FOR DIAGNOSING AND TREATING HEART DISEASE

### Field of the Invention

5           This invention relates to methods for diagnosing and treating heart disease.

### Background of the Invention

Heart disease is a general term used to describe many different heart conditions. For example, coronary artery disease, which is the most  
10 common heart disease, is characterized by constriction or narrowing of the arteries supplying the heart with oxygen-rich blood, and can lead to myocardial infarction, which is the death of a portion of the heart muscle. Heart failure is a condition resulting from the inability of the heart to pump an adequate amount of blood through the body. Heart failure is not  
15 a sudden, abrupt stop of heart activity, but, rather, typically develops slowly over many years, as the heart gradually loses its ability to pump blood efficiently. Risk factors for heart failure include coronary artery disease, hypertension, valvular heart disease, cardiomyopathy, disease of the heart muscle, obesity, diabetes, and a family history of heart failure.

### Summary of the Invention

20           The invention provides diagnostic, drug screening, and therapeutic methods based on the observation that mutation of the *titin* gene leads to a phenotype in zebrafish that is similar to mammalian heart failure.

In one aspect, the invention provides a method of determining whether a test subject (*e.g.*, a mammal, such as a human) has, or is at risk of developing, a titin-related disease or condition (*e.g.*, heart failure). This method involves analyzing a nucleic acid molecule of a sample from the  
5 test subject to determine whether the test subject has a mutation (for example, a mutation in a cardiac-specific exon, such as the N2B exon; *e.g.*, the *pickwick* mutation; see below) in a *titin* gene. The presence of such a mutation is an indication that the test subject has, or is at risk of developing, a titin-related disease. This method can further involve using  
10 nucleic acid molecule primers specific for the *titin* gene for nucleic acid molecule amplification of the *titin* gene by the polymerase chain reaction, or sequencing *titin* nucleic acid molecules from the test subject.

In another aspect, the invention provides a screening method for identifying a compound that can be used to treat or to prevent heart failure.  
15 This method involves contacting an organism (*e.g.*, a zebrafish) having a *titin* mutation (for example, a mutation in a cardiac-specific exon, such as the N2B exon; *e.g.*, the *pickwick* mutation) and a phenotype characteristic of heart failure with the compound, and determining the effect of the compound on the phenotype. Detection of an improvement in the  
20 phenotype indicates the identification of a compound that can be used to treat or to prevent heart failure.

In another aspect, the invention provides a method of treating or preventing heart disease, such as heart failure, in a patient. This method involves administering to the patient a compound identified using the  
25 screening method described above. A patient treated using this method can have a mutation in the *titin* gene.

In a further aspect, the invention provides a non-human animal (*e.g.*, a zebrafish or a mouse) that has a mutation in a *titin* gene. The

mutation can be, for example, in a cardiac-specific exon of the *titin* gene, such as the N2B exon, and can result in production of a truncated titin product, for example, by the introduction of a stop codon.

By “polypeptide” or “polypeptide fragment” is meant a chain of  
5 two or more amino acids, regardless of any post-translational modification (*e.g.*, glycosylation or phosphorylation), constituting all or part of a naturally or non-naturally occurring polypeptide. By “post-translational modification” is meant any change to a polypeptide or polypeptide fragment during or after synthesis. Post-translational modifications can be  
10 produced naturally (such as during synthesis within a cell) or generated artificially (such as by recombinant or chemical means). A “protein” can be made up of one or more polypeptides.

By “titin,” “titin protein,” or “titin polypeptide” is meant a polypeptide that has at least 45%, preferably at least 60%, more preferably  
15 at least 75%, and most preferably at least 90% amino acid sequence identity to the sequence of the human (see below) or the zebrafish titin polypeptides. Polypeptide products from splice variants of *titin* gene sequences and *titin* genes containing mutations are also included in this definition. A titin polypeptide as defined herein plays a role in heart  
20 development, modeling, structure, and contractility. It can be used as a marker of heart disease, such as heart failure.

By a “*titin* nucleic acid molecule” is meant a nucleic acid molecule, such as a genomic DNA, cDNA, or RNA (*e.g.*, mRNA) molecule, that encodes titin, a titin protein, a titin polypeptide, or a portion thereof, as  
25 defined above.

The term “identity” is used herein to describe the relationship of the sequence of a particular nucleic acid molecule or polypeptide to the sequence of a reference molecule of the same type. For example, if a

polypeptide or nucleic acid molecule has the same amino acid or nucleotide residue at a given position, compared to a reference molecule to which it is aligned, there is said to be “identity” at that position. The level of sequence identity of a nucleic acid molecule or a polypeptide to a  
5 reference molecule is typically measured using sequence analysis software with the default parameters specified therein, such as the introduction of gaps to achieve an optimal alignment (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705,  
10 BLAST, or PILEUP/PRETTYBOX programs). These software programs match identical or similar sequences by assigning degrees of identity to various substitutions, deletions, or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine, valine, isoleucine, and leucine; aspartic acid, glutamic  
15 acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine.

A nucleic acid molecule or polypeptide is said to be “substantially identical” to a reference molecule if it exhibits, over its entire length, at least 51%, preferably at least 55%, 60%, or 65%, and most preferably  
20 75%, 85%, 90%, or 95% identity to the sequence of the reference molecule. For polypeptides, the length of comparison sequences is at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably at least 35 amino acids. For nucleic acid molecules, the length of comparison sequences is at least 50  
25 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably at least 110 nucleotides.

A *titin* nucleic acid molecule or *titin* polypeptide is “analyzed” or subject to “analysis” if a test procedure is carried out on it that allows the

determination of its biological activity or whether it is wild type or mutated. For example, one can analyze the *titin* genes of an animal (*e.g.*, a human or a zebrafish) by amplifying genomic DNA of the animal using the polymerase chain reaction, and then determining whether the amplified  
5 DNA contains a mutation, for example, the *pickwick* mutation, by, *e.g.*, nucleotide sequence or restriction fragment analysis.

By “probe” or “primer” is meant a single-stranded DNA or RNA molecule of defined sequence that can base pair to a second DNA or RNA molecule that contains a complementary sequence (“target”). The stability  
10 of the resulting hybrid depends upon the extent of the base pairing that occurs. This stability is affected by parameters such as the degree of complementarity between the probe and target molecule, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as the temperature, salt  
15 concentration, and concentration of organic molecules, such as formamide, and is determined by methods that are well known to those skilled in the art. Probes or primers specific for *titin* nucleic acid molecules, preferably, have greater than 45% sequence identity, more preferably at least 55-75% sequence identity, still more preferably at least 75-85% sequence identity,  
20 yet more preferably at least 85-99% sequence identity, and most preferably 100% sequence identity to the sequences of human (see below) or zebrafish *titin*.

Probes can be detectably-labeled, either radioactively or non-radioactively, by methods that are well-known to those skilled in the art.  
25 Probes can be used for methods involving nucleic acid hybridization, such as nucleic acid sequencing, nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern

hybridization, northern hybridization, *in situ* hybridization, electrophoretic mobility shift assay (EMSA), and other methods that are well known to those skilled in the art.

A molecule, *e.g.*, an oligonucleotide probe or primer, a gene or  
5 fragment thereof, a cDNA molecule, a polypeptide, or an antibody, can be said to be “detectably-labeled” if it is marked in such a way that its presence can be directly identified in a sample. Methods for detectably-labeling molecules are well known in the art and include, without  
10 limitation, radioactive labeling (*e.g.*, with an isotope, such as  $^{32}\text{P}$  or  $^{35}\text{S}$ ) and nonradioactive labeling (*e.g.*, with a fluorescent label, such as fluorescein).

By a “substantially pure polypeptide” is meant a polypeptide (or a fragment thereof) that has been separated from proteins and organic molecules that naturally accompany it. Typically, a polypeptide is  
15 substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the polypeptide is a titin polypeptide that is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure titin polypeptide can be obtained, for  
20 example, by extraction from a natural source (*e.g.*, isolated heart tissue), by expression of a recombinant nucleic acid molecule encoding a titin polypeptide, or by chemical synthesis. Purity can be measured by any appropriate method, *e.g.*, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

25 A polypeptide is substantially free of naturally associated components when it is separated from those proteins and organic molecules that accompany it in its natural state. Thus, a protein that is chemically synthesized or produced in a cellular system different from the

cell in which it is naturally produced is substantially free from its naturally associated components. Accordingly, substantially pure polypeptides not only include those derived from eukaryotic organisms, but also those synthesized in *E. coli* or other prokaryotes.

5           An antibody is said to “specifically bind” to a polypeptide if it recognizes and binds to the polypeptide (*e.g.*, a titin polypeptide), but does not substantially recognize and bind to other molecules (*e.g.*, non-titin related polypeptides) in a sample, *e.g.*, a biological sample that naturally includes the polypeptide.

10           By “high stringency conditions” is meant conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M NaHPO<sub>4</sub>, pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V), at a temperature of 65°C, or a buffer containing 48% formamide, 4.8 x SSC,  
15 0.2 M Tris-Cl, pH 7.6, 1 x Denhardt’s solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42°C. (These are typical conditions for high stringency northern or Southern hybridizations.) High stringency hybridization is also relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR,  
20 DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to northern and Southern hybridizations, these techniques are usually performed with relatively short probes (*e.g.*, usually 16 nucleotides or longer for PCR or sequencing and 40 nucleotides or longer for *in situ* hybridization). The high  
25 stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and examples of them can be



found, for example, in Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1998, which is hereby incorporated by reference.

By “sample” is meant a tissue biopsy, amniotic fluid, cell, blood,  
5 serum, urine, stool, or other specimen obtained from a patient or test subject. The sample can be analyzed to detect a mutation in a *titin* gene, or expression levels of a *titin* gene, by methods that are known in the art. For example, methods such as sequencing, single-strand conformational polymorphism (SSCP) analysis, or restriction fragment length  
10 polymorphism (RFLP) analysis of PCR products derived from a patient sample can be used to detect a mutation in a *titin* gene; ELISA can be used to measure levels of titin polypeptide; and PCR can be used to measure the level of a *titin* nucleic acid molecule.

By “titin-related disease” or “titin-related condition” is meant a  
15 disease or condition that results from inappropriately high or low expression of a *titin* gene, or a mutation in a *titin* gene that alters the biological activity of a *titin* nucleic acid molecule or polypeptide. Titin-related diseases and conditions can arise in any tissue in which titin is expressed during prenatal or post-natal life. Titin-related diseases and  
20 conditions can include heart diseases, such as heart failure. Specific examples of different types of heart failure are provided below.

The invention provides several advantages. For example, using the diagnostic methods of the invention, it is possible to detect an increased likelihood of heart disease, such as heart failure, in a patient, so that  
25 appropriate intervention can be instituted before any symptoms occur. This may be useful, for example, with patients in high-risk groups for heart failure (see above). Also, the diagnostic methods of the invention facilitate determination of the etiology of an existing heart condition, such

as heart failure, in a patient, so that an appropriate approach to treatment can be selected. In addition, the screening methods of the invention can be used to identify compounds that can be used to treat or to prevent heart conditions, such as heart failure.

- 5           Other features and advantages of the invention will be apparent from the following detailed description and the claims.

### Brief Description of the Drawing

Fig. 1 is a schematic representation of the domain structure of the human titin filament. The nucleotide and amino acid sequences of human  
10 titin are provided in SEQ ID NOs:1 and 2, respectively. The modular architecture of cardiac titin as predicted by its full-length cDNA is shown.

- A total of 244 copies of 100 residue repeats, as indicated by vertical rectangles, are contained in the molecule. One hundred and twelve of these belong to the Ig domain, and 132 belong to the FN3 superfamily.
- 15 The titin kinase domain, as well as the PEVK element N2-B 163-residue variant are also shown. Within the A-band, the D-zone contains six tandem repeats of the seven domains shown (A1 through A42), and the C-zone contains 11 tandem repeats of the 11 domains shown (A43 through A163). The positions of the tandemly repeated RMSP and VKSP motifs  
20 in the Z-disc and M-line region are also shown

### Detailed Description

The invention provides methods of diagnosing heart disease, screening methods for identifying compounds that can be used to treat or to prevent heart disease, and methods of treating or preventing heart

disease using these compounds. The invention also provides animal model systems that can be used in the screening methods of the invention.

In particular, we have discovered that a mutation (the *pickwick* mutation) in the *titin* gene is associated with heart disease, such as heart failure. Titin, which is also known as “connectin,” is the largest known single-chain protein, having a molecular weight of about 3,000 kDa. Titin is a structural protein, and plays a central role in the assembly and elasticity of vertebrate skeletal and cardiac muscle. Thus, the diagnostic methods of the invention involve detection of mutations in the *titin* gene, while the compound identification methods of the invention involve screening for compounds that affect the phenotype of *titin* mutants or other models of heart disease, such as heart failure. Compounds identified in this manner can be used in methods to treat or to prevent heart disease (*e.g.*, heart failure). The diagnostic, screening, and therapeutic methods of the invention, as well as the animal model systems of the invention, are described further, as follows.

#### Diagnostic Methods

*Titin* nucleic acid molecules, polypeptides, and antibodies can be used in methods to diagnose or to monitor diseases and conditions involving mutations in, or inappropriate expression of, *titin* genes. As discussed further below, the *pickwick* mutation in zebrafish, which is present in the *titin* gene, is characterized by a phenotype that is similar to that of heart failure in humans. Thus, detection of abnormalities in *titin* genes or their expression can be used in methods to diagnose, or to monitor treatment or development of, human heart disease, such as heart failure. For use as references, the human cardiac *titin* cDNA sequence can be found at:

<http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacseq.html> (SEQ ID NO:1), while the corresponding protein sequence can be found at: <http://www.embl-heidelberg.de/ExternalInfo/Titin/cardiacpep.html> (SEQ ID NO:2).

5           As noted above, the diagnostic methods of the invention can be used, for example, with patients that have heart failure, in an effort to determine its etiology and, thus, to facilitate selection of an appropriate course of treatment. The diagnostic methods can also be used with patients that have not yet developed heart failure, but who are at risk of  
10   developing such a disease, or with patients that are at an early stage of developing such a disease. Also, the diagnostic methods of the invention can be used in prenatal genetic screening, for example, to identify parents who may be carriers of a recessive *titin* mutation.

          Examples of heart failure that can be diagnosed (and treated) using  
15   the methods of the invention include congestive heart failure, which is characterized by fluid in the lungs or body, resulting from failure of the heart in acting as a pump; right sided heart failure (right ventricular), which is characterized by failure of the pumping action of the right ventricle, resulting in swelling of the body, especially the legs and  
20   abdomen; left sided heart failure (left ventricular), which is caused by failure of the pumping action of the left side of the heart, resulting in congestion of the lungs; forward heart failure, which is characterized by the inability of the heart to pump blood forward at a sufficient rate to meet the oxygen needs of the body at rest or during exercise; backward heart  
25   failure, which is characterized by the ability of the heart to meet the needs of the body only if heart filling pressures are abnormally high; low-output,

which is characterized by failure to maintain blood output; and high-output, which is characterized by heart failure symptoms, even when cardiac output is high.

Titin may also play a role in cardiovascular diseases other than heart failure, such as coronary artery disease or conditions associated with valve formation defects, and, thus, detection of abnormalities in *titin* genes or their expression can be used in methods to diagnose and monitor these conditions as well. The methods of the invention can be used to diagnose (or to treat) the disorders described herein in any mammal, for example, humans, domestic pets, or livestock.

Titin abnormalities that can be detected using the diagnostic methods of the invention include those characterized by, for example, (i) abnormal titin polypeptides, (ii) *titin* genes containing mutations that result in the production of such polypeptides, and (iii) *titin* mutations that result in production of abnormal amounts of titin. Detection of such abnormalities, thus, can be used in methods to diagnose human heart disease, such as heart failure. Exemplary of the *titin* mutations that can be detected using the methods of the invention is the *pickwick* mutation (see below).

Detection of *titin* mutations can be carried out using any diagnostic technique. For example, a biological sample obtained from a patient can be analyzed for one or more mutations in *titin* nucleic acid molecules (e.g., the *pickwick* mutation) using a mismatch detection approach. Generally, this approach involves polymerase chain reaction (PCR) amplification of nucleic acid molecules from a patient sample, followed by identification of a mutation (i.e., a mismatch) by detection of altered hybridization, aberrant electrophoretic gel migration, binding, or cleavage mediated by mismatch binding proteins, or by direct nucleic acid molecule sequencing. Any of

these techniques can be used to facilitate detection of mutant *titin* genes, and each is well known in the art. Examples of these techniques are described by Orita *et al.* (Proc. Natl. Acad. Sci. U.S.A. 86:2766-2770, 1989) and Sheffield *et al.* (Proc. Natl. Acad. Sci. U.S.A. 86:232-236, 5 1989).

Mutation detection assays also provide an opportunity to diagnose a titin-mediated predisposition to heart disease before the onset of symptoms. For example, a patient heterozygous for a *titin* mutation that suppresses normal titin biological activity or expression may show no 10 clinical symptoms of a titin-related disease, and yet possess a higher than normal probability of developing heart disease, such as heart failure. Given such a diagnosis, a patient can take precautions to minimize exposure to adverse environmental factors, and can carefully monitor their medical condition, for example, through frequent physical examinations. 15 As mentioned above, this type of diagnostic approach can also be used to detect *titin* mutations in prenatal screens.

The *titin* diagnostic assays described above can be carried out using any biological sample (for example, a muscle tissue sample) in which titin is normally expressed. Because of the limited number of tissues in which 20 titin is expressed, as well as the relative difficulties involved in obtaining samples of these tissues, it may be preferable to detect mutant *titin* genes in another, more easily obtained sample type, such as blood or amniotic fluid samples using, for example, mismatch detection techniques. Preferably, the DNA in such a sample is subjected to PCR amplification 25 prior to analysis.

Levels of titin expression in a patient sample can be determined by using any of a number of standard techniques that are well known in the art. For example, titin expression in a biological sample (*e.g.*, a blood or

tissue sample, or amniotic fluid) from a patient can be monitored by standard northern blot analysis or by quantitative PCR (see, *e.g.*, Ausubel *et al.*, *supra*; *PCR Technology: Principles and Applications for DNA Amplification*, H.A. Ehrlich, Ed., Stockton Press, NY; Yap *et al.*, Nucl. Acids. Res. 19:4294, 1991).

In yet another diagnostic approach of the invention, an immunoassay is used to detect or to monitor titin protein levels in a biological sample. Titin-specific polyclonal or monoclonal antibodies can be used in any standard immunoassay format (*e.g.*, ELISA, Western blot, or RIA; see, *e.g.*, Ausubel *et al.*, *supra*) to measure titin polypeptide levels. These levels are compared to wild-type titin levels. For example, a decrease in titin production may be indicative of a condition or a predisposition to a condition involving insufficient titin biological activity.

Immunohistochemical techniques can also be utilized for titin detection. For example, a tissue sample can be obtained from a patient, sectioned, and stained for the presence of titin using an anti-titin antibody and any standard detection system (*e.g.*, one that includes a secondary antibody conjugated to horseradish peroxidase). General guidance regarding such techniques can be found in, *e.g.*, Bancroft *et al.*, *Theory and Practice of Histological Techniques*, Churchill Livingstone, 1982, and in Ausubel *et al.*, *supra*.

#### Identification of Molecules That Can Be Used to Treat or to Prevent Heart Failure

Identification of a mutation in *titin* as resulting in a phenotype that is related to heart failure facilitates the identification of molecules (*e.g.*, small organic molecules, peptides, or nucleic acid molecules) that can be

used to treat or to prevent heart failure. The effects of candidate compounds on heart failure can be investigated using, for example, the zebrafish system. The zebrafish, *Danio rerio*, is a convenient organism to use in genetic analysis of vascular development. In addition to its short  
5 generation time and fecundity, it has an accessible and transparent embryo, allowing direct observation of blood vessel function from the earliest stages. As discussed further below, zebrafish and other animals having mutations in the *titin* gene, which can be used in these methods, are also included in the invention.

10 In one example of the screening methods of the invention, a zebrafish having a mutation in the *titin* gene (*e.g.*, a zebrafish having the *pickwick* mutation; see below) is contacted with a candidate compound, and the effect of the compound on the development of a heart abnormality that is characteristic of heart failure, or on the status of such an existing  
15 heart abnormality, is monitored, relative to an untreated, identically mutant control. As discussed further below, zebrafish having the *pickwick* mutation are characterized by, for example, reduction of peak systolic pressures, stretched and thin myocardium, excess cardiac jelly, absent A-V cushions, and an obstructed ventricular outflow tract. Thus, these  
20 characteristics (in addition to other characteristics of heart failure) can be monitored using the screening methods of the invention.

After a compound has been shown to have a desired effect in the zebrafish system, it can be tested in other models of heart disease, for example, in mice or other animals having a mutation in the *titin* gene.  
25 Alternatively, testing in such animal model systems can be carried out in the absence of zebrafish testing.

Candidate compounds can be purified (or substantially purified) molecules or can be one component of a mixture of compounds (*e.g.*, an



extract or supernatant obtained from cells; Ausubel *et al.*, *supra*). In a mixed compound assay, the effect on a phenotype of heart failure is tested against progressively smaller subsets of the candidate compound pool (*e.g.*, produced by standard purification techniques, *e.g.*, HPLC or FPLC) until a single compound or minimal compound mixture is demonstrated to have the desired effect.

Test compounds that can be screened in the methods described above can be chemicals that are naturally occurring or artificially derived. Such compounds can include, for example, polypeptides, synthesized organic molecules, naturally occurring organic molecules, nucleic acid molecules, and components thereof. Candidate compound can be found, for example, in a cell extract, mammalian serum, or growth medium in which mammalian cells have been cultured.

In general, novel drugs for prevention or treatment of mutant titin-related heart diseases can be identified from large libraries of both natural products, synthetic (or semi-synthetic) extracts, and chemical libraries using methods that are well known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening methods of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using these methods. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic-, or animal-based extracts, fermentation broths, and synthetic compounds, as well as modifications of existing compounds.

Numerous methods are also available for generating random or directed synthesis (*e.g.*, semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid molecule-based compounds. Synthetic

compound libraries are commercially available from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographic Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries can be produced, if desired, according to methods known in the art, *e.g.*, by standard extraction and fractionation. Furthermore, if desired, any library or compound can be readily modified using standard chemical, physical, or biochemical methods.

In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (*e.g.*, taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their therapeutic activities for heart failure can be employed whenever possible.

When a crude extract is found to have an effect on the development or persistence of heart failure, further fractionation of the positive lead extract can be carried out to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having a desired activity. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives of these compounds. Methods of fractionation and purification of such heterogeneous extracts are well known in the art. If desired,

compounds shown to be useful agents for treatment can be chemically modified according to methods known in the art.

#### Treatment or Prevention of Heart Failure

Compounds identified using the screening methods described above  
5 can be used to treat patients that have or are at risk of developing heart disease, such as heart failure. Such treatment may be required only for a short period of time, or may, in some form, be required throughout a patient's lifetime. Any continued need for treatment, however, can be determined using, for example, the diagnostic methods described above.  
10 In considering various therapies, it is understood that such therapies are, preferably, targeted to the affected or potentially affected organ, that is, the heart.

Treatment or prevention of diseases resulting from a mutated *titin* gene can be accomplished, for example, by modulating the function of a  
15 mutant titin protein, delivering normal titin protein to the appropriate cells, altering the levels of normal or mutant titin protein, replacing a mutant *titin* gene with a normal *titin* gene or, administering a normal *titin* gene. It is also possible to correct a *titin* defect by modifying the physiological pathway (*e.g.*, a signal transduction pathway) in which the titin protein  
20 participates.

In a patient diagnosed as heterozygous for a *titin* mutation, or as susceptible to *titin* mutations or aberrant titin expression (even if those mutations or expression patterns do not yet result in alterations in titin expression or biological activity), any of the above-described therapies can  
25 be administered before the occurrence of the disease phenotype. In particular, compounds shown to modulate titin expression or to have an

effect on the phenotype of *titin* mutants can be administered to patients diagnosed with potential or actual heart disease by any standard dosage and route of administration.

Any appropriate route of administration can be employed to  
5 administer a compound found to be effective in treating or preventing heart failure, according to the invention. For example, administration can be parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, or oral. However, as noted above, preferably, the  
10 administration is local to the afflicted tissue, that is, the heart. Therapeutic formulations can be in the form of liquid solutions or suspensions; for oral administration, formulations can be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

15 A therapeutic compound of the invention can be administered within a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration can begin before or after the patient is symptomatic. Methods that are well known in the art for making formulations are found, for example, in *Remington's Pharmaceutical*  
20 *Sciences*, (18<sup>th</sup> edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA. Formulations for parenteral administration can, for example, contain excipients; sterile water; or saline; polyalkylene glycols, such as polyethylene glycol; oils of vegetable origin; or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide  
25 copolymer, or polyoxyethylene-polyoxypropylene copolymers can be used to control the release of the compounds. Other potentially useful parenteral delivery systems for compounds identified using the methods of the invention include ethylene-vinyl acetate copolymer particles, osmotic

pumps, implantable infusion systems, and liposomes. Formulations for inhalation can contain excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate, and deoxycholate, or can be oily solutions for administration  
5 in the form of nasal drops, or as a gel.

*Titin* nucleic acid molecules and polypeptides can also be used in tissue engineering, for example, in the manufacture of artificial or partially artificial hearts. As mentioned above, titin plays a role in cardiovascular elasticity, integrity, and contractility. Thus, a *titin* nucleic acid molecule  
10 or polypeptide, as described above, can be used to impart such characteristics on an artificial or partially artificial heart.

#### Animal Model Systems

The invention also provides animal model systems for use in carrying out the screening methods described above. Examples of these  
15 model systems include zebrafish and other animals, such as mice, that have mutations in a *titin* gene. For example, a zebrafish model that can be used in the invention can include a mutation that results in a lack of titin production or production of a truncated (*e.g.*, by introduction of a stop codon) or otherwise altered titin gene product. The mutation can, for  
20 example, result in the presence of a stop codon in a cardiac-specific exon, such as the N2B exon (*e.g.*, in the IS3 region; see below). The mutation can be in a region encoding the I band, resulting in the production of a protein in which the I band is truncated and the A band and M line are absent, or can be in a region encoding another portion of the molecule,  
25 such as the A band or M line region. As a specific example, a zebrafish having the *pickwick* mutation can be used.

### Experimental Results

During a large-scale mutagenesis screening of the zebrafish genome, a group of mutations were identified that affect cardiac contractility. One of these mutations, called *pickwick* (*pik*), dramatically  
5 reduces the function of both chambers, causing a recessive, lethal form of heart failure in the zebrafish embryo.

Direct *in vivo* recording of ventricular pressures by the null balance feedback system shows that *pickwick* causes a 5.8 fold reduction of peak systolic pressures, compared to age-matched controls ( $0.084 \pm 0.008$  vs.  
10  $0.49 \pm 0.06$  mm Hg). Morphological analysis of *pickwick* revealed a stretched and thin myocardium, excess cardiac jelly, absent A-V cushions, and an obstructed ventricular outflow tract. Extensive ultrastructural defects were found by transmission electron microscopy, affecting the assembly of Z-discs and the organization of myofilaments. Reciprocal  
15 blastomere transplants identified *pickwick* as a cell autonomously acting mutation of the myoblast lineage.

A positional cloning approach was adopted for gene identification. The *pickwick* mutation has been assigned to a small chromosomal interval, which is covered by BAC clones. The *titin* gene spans this interval, and  
20 thus the *pickwick* phenotype is due to a mutation in the *titin* gene. In particular, the *pickwick* gene was mapped to linkage group (LG) 9 by bulk segregant analysis using the *pikm242* allele, which is one of five cardiac specific alleles (*pikm242*, *pikm171*, *pikm740*, *pikm186*, *pikmnm2*). A panel of Z-markers in the linkage group was tested for simple sequence  
25 length polymorphisms (SSLPs) using 931 homozygous mutant embryos. Markers Z8363 and Z26463 were shown to flank the *pickwick* locus, defining a 1.2 cM interval containing the gene. It is estimated that 1 cM corresponds to 500-600 kb DNA in the zebrafish genome (Postlethwait *et*

*al.*, Science 264:699-703, 1994). We thus initiated chromosomal walking from the Z8363 marker, which is 0.7 cM from the mutation (12 recombinants out of 1750 meioses).

A positive YAC clone (YAC5) was identified that had a T7 end that  
5 is highly homologous to human *titin* coding sequences. As the *titin* genomic region was estimated to be over 300 kb in humans, we decided to identify BAC clones based on sequence information of the zebrafish *titin* EST clones. A physical contig was constructed based on these sequences, which covers the whole *titin* genomic area. Single stranded  
10 conformational polymorphisms (SSCPs) were developed from the ends and internal sequences of these clones were used for fine recombinational mapping. One SSCP marker inside the *titin* genomic area (B9F2) picked up one recombinant from the Z26463 side. The other four SSCP markers inside the *titin* genomic area (B4SP1, B2T7, B7SP, and B6SP) picked up  
15 zero recombinants out of 1750 meioses. These genetic data indicated that the *pickwick* locus is very close to or within the *titin* genomic region.

As the *titin* cDNA alone is around 82 kb, rescuing the phenotype by RNA injection could prove to be quite difficult. However, we found evidence that the *pickwick* locus is within the *titin* gene by identification of  
20 point mutations in one of the *pickwick* alleles. As most of the alleles of *pickwick* have a cardiac-specific phenotype, we presumed that the point mutation is located in a cardiac-specific exon. We focused on the N2B domain in the I-band of titin, as all of the cardiac isoforms are N2B domain based. The zebrafish N2B domain was cloned by RT-PCR. It is a  
25 4.3 kb cDNA encoding infrastructures similar to those in humans and mice, and contains 4 IG repeats and three unique sequences, including longer IS3 and shorter IS1.

N2B domains from *pickwick* mutant embryos were then cloned. RNA mismatch analysis was performed to identify the location of the point mutation. One mismatch between the PCR products from *pikm171* and *pikm242* was identified. Sequencing of the PCR product resulted in the identification of a T-> G transition in the *pikm171* allele. This mutation resulted in a change of leucine in the IS3 fragment of N2B domain (N2B-IS3) into a stop codon. The mutation was confirmed in all of the seven homozygous *pikm171* mutant embryos, but none of the four *pikm242* homozygous embryos. A truncated version of titin is predicted to be in the *pikm171* mutant, only as a cardiac specific isoform. It should contain the Z-disc and part of the I-band and be sized around 4,000 amino acids, based on comparison to the homologous human titin sequence, which has a full length of 27,000 amino acids. The identification of a non-sense mutation in the cardiac specific N2B domain in *pikm171* allele confirmed the hypothesis that *titin* is the *pickwick* gene.

Titin was expressed in the zebrafish embryo during the period when the *pickwick* phenotype was first detected. Whole mount *in situ* hybridization analysis indicated that *titin* was expressed strongly in both the heart and the somites at 24 hpf. *Titin* mRNA expression in the heart is normal in *pikm171*. We confirmed the notion that N2B is a cardiac-specific exon in zebrafish by labeling a probe in the IS3 domain for the whole mount *in situ* hybridization.

The identification of a point mutation in the N2B domain thus establishes *pickwick* as the first *in vivo* vertebrate system to study the functions of titin in the heart. If titin functions as a spring, as proposed, it is expected that the contraction will be much weaker. This is exactly what we observed in *pickwick* mutant embryos. If titin functions as a template during the sarcomere assembly, a “silent heart” phenotype would be



expected in titin null mutation. According to the current model of the myofibrillogenesis (Dabiri *et al.*, Proc. Natl. Acad. Sci. U.S.A. 94:9493-9498, 1997), the thick element and/or the sarcomere could not assemble into a beating machine. In contrast, the hearts in the homozygous *pikm171* mutant embryos and all of the other *pickwick* alleles still beat, despite being weaker.

The mutation in *pikm171* predicts a truncated protein in which most of the elastic I-band is deleted and the C-terminal A-band and M-line regions eliminated. It thus could be considered as a null mutation in terms of function as a spring and a potential dominant negative mutation in terms of its function as a template for sarcomere assembly (Turnacioglu *et al.*, Mol. Biol. Cell 8:705-717, 1997). The observation of the weak beating in the *pickwick* mutant embryos suggested the existence of primary contractile machinery without titin. Indeed, thick and thin elements can be detected in the ventricular myocardium cells. They have the capacity to assemble into a functional beating structure in the absence of titin.

We thus have carried out a detailed physiological and morphological analysis of *pickwick*, a zebrafish heart function mutation that reduces the contractility of both chambers. Several pieces of evidence pointed out that *titin* is the *pickwick* gene. Genetic analysis linked the *pickwick* locus closely to the *titin* genomic area. The identification of the *pikmVO62H*, a *pickwick* allele that has an additional somite phenotype, can be explained by the titin hypothesis. The point mutation is expected to be in the common exons that are shared between the cardiac and somatic isoforms of titin. Evidence confirming this hypothesis came from the identification of a point mutation in the cardiac specific N2B domain of titin in one of the *pickwick* alleles, *pikm171*. We went on to show that sarcomere structure is disrupted in the myocardium cells of *pikm171*, but

not the somatic muscle cells. The expression pattern of titin is consistent with this phenotype. Strong expression in both cardiac and skeletal muscles was detected at the onset of the *pickwick* phenotype.

Thus, our observation in zebrafish is in consistent with the notion  
 5 that titin functions as a spring during the muscle contraction. As titin is a sarcomere structure protein, it is conceivable that myocardium is affected cell-autonomously in *pickwick* mutant embryos. The thin and stretched morphology could be due to the mechanic tension generated from the failure to form higher-order sarcomere structure and the loss of spring.  
 10 The mechanic tension may also be the reason for the separation between the myocardium cells and endocardium cells, generating the excess cardiac jelly. However, there is a possibility that the differentiation program of the myocardium was affected in the *titin* mutation. The valve formation phenotype in *pickwick* mutant embryos could be a secondary defect. It has  
 15 been suggested that the process of endothelial invasion during valve formation is under control of a localized myocardial signal. (For a review, see Fishman *et al.*, Development 124:2099-2117, 1997.) The physical distance between myocardium and endocardium and/or the stalked differential program in the myocardium could be the reason that prevents a  
 20 normal cushion formation.

## Material and Methods

### Zebrafish strains and maintenance

Zebrafish were maintained and staged as described. *pikm242*,  
*pikm171*, *pikm740*, *pikm186* were generated in a screen on the AB  
 25 background (Stainier *et al.*, Development 123:285-292, 1996).  
*pikmVO62H* and *pikmnml2* were generated in a screen on the TL background. Mapping strains were constructed by crossing *pikm242* into

india strain. *pikm171* embryos used in expression analysis and EM were obtained from pair wise matings of *pikm171*/TL heterozygotes.

#### In situ hybridization

Whole mount *in situ* hybridization was performed as described  
5 (Thisse *et al.*, Development 119:1203-1215, 1993). T5 probe was generated by digestion of the EST clone AI629069 (Research Genetics). The N2B and N2A probe were generated through PCR with a tagged T7 promoter. The primer pairs are:  
P238F: 5'-AGGGACACTCAGAGACCATAG (SEQ ID NO:3); and  
10 P3785RT: 5'-  
TAATACGACTCACTATAGGGGTCTGAGGATACTCGCCTTC (SEQ ID NO:4).

#### Mapping of *pickwick*

Linkage was established using DNA from 16 homozygous  
15 mutations and 16 heterozygous or wild type pick *pikm242*/indian embryos in bulk segregation analysis (Michelmore *et al.*, Proc. Natl. Acad. Sci. U.S.A. 88:9828-9832, 1991). Z-markers (simple sequence length polymorphisms, SSLP) were developed in this lab (Knapik *et al.*, Nat. Genet. 18:338-343, 1998; Shimoda *et al.*, Genomics 58:219-232, 1999).  
20 Genotyping products were resolved in 6% PAGE gels.

#### Chromosomal walking

YAC and BAC clones were screened by PCR as pools of clones (Research Genetics) according to the manufacturer's instruction. YAC ends were cloned by plasmid rescue (Zhong *et al.*, Genomics 48:136-138,  
25 1998). Chimeric ends were determined by the RH panel (Geisler *et al.*,

Nat. Genet. 23:86-89, 1999). BAC DNA was extracted using the QIAgene kit and the end sequences were determined by direct sequencing. BLAST-X was performed to search for homologous sequence in Genbank. EST clones were generated by Washington University zebrafish EST project  
5 and obtained from Research Genetics. Oligonucleotides derived from the end sequences of YAC and BAC clones were used in standard PCR reactions to determine clone overlap. Primer pair B9F2 was derived from a fragment that was generated by digesting BAC5 with BamHI and then subcloning into the pUC19 vector. This clone can be hit by a primer pair  
10 derived from the T7 end of BAC7. Single-strand conformation polymorphisms (SSCP) were tested on 6% MDE acrylamide (FMC Bioproducts) gels at 40°C.

#### Cloning of the zebrafish N2B domain

Long RT-PCR was performed to amplify the N2B domain from  
15 adult zebrafish heart mRNA extracts. mRNA was extracted from pools of ten zebrafish adult hearts using TRIzol reagent (GibcoBRL), as described. The cDNA was synthesized using SuperScriptTMII RNase H-Reverse Transcriptase (GibcoBRL) and then treated with RNase H. The primer is derived from EST3: I19R1:

20 5'- TTTGAACCACTTGAAGGTCACACCAGG (SEQ ID NO:5).

Long-PCR was performed using Expand 20kbPlus PCR System (Roch) as described. The primer pairs are:

I14F1: 5'- GCTAAGAATGACTATGGAGTTGCCACAAGC (SEQ ID NO:6)

25 I19R2: 5'- TGAACCACTTGAAGGTCACACCAGGAG (SEQ ID NO:7)

The 4.6 kb product was subcloned using TOPO TA Cloning Kit (Invitrogen) as described. The sequence was determined by primer walking. Forty eight reads were aligned by Phred/Phrad software to get a large contig that contains only one reading frame with around three fold  
5 coverage.

To amplify the N2B region from the homozygous mutant zebrafish embryos, three overlapping primer pairs were designed according to the adult N2B sequence. The contamination from the skeletal muscle specific titin isoform was thus eliminated. mRNA was extracted from pools of ten  
10 zebrafish day 2 embryos using TRIzol reagent (GibcoBRL) as described. Sequencing results indicated that the embryonic heart titin contain one less IG domain in the area.

#### Identification of the point mutation

N2B domains from the homozygous mutant embryos were further  
15 amplified by primer pairs that generate six overlapping PCR products sized between 0.6 kb and about 1 kb. RNA mismatch analysis was performed using MutationScreener™ (Ambion) according to the manufacture's protocol. A mismatch was identified between *pikm171* and *pikm242* using the primer pairs:

20 P238FT:

5'-TAATACGACTCACTATAGGGAGGGACACTCAGAGACCATAG  
(SEQ ID NO:8)

P3785RT: 5'-

TAATACGACTCACTATAGGGGTCTGAGGATACTCGCCTTC (SEQ  
25 ID NO:9). Sequencing results indicate a T->G non-sense mutation in the cDNA from homozygous *pikm171* embryos.

Genomic sequence in this region was amplified using the primer pair:

P238F: 5'-AGGGACACTCAGAGACCATAG (SEQ ID NO:10)

P341R: 5'- GGCAATGTTACTCTCTGTTGAG (SEQ ID NO:11)

and sent out directly for sequencing after purification using the Geneclean Spin Kit (BIO101).

5 Electron Microscopy

Forty eight hour embryos were fixed overnight at 4°C in 1.5% glutaraldehyde, 1% paraformaldehyde, 70 mM NaPO<sub>4</sub> pH 7.2, 3% Sucrose. They were then washed 3 times for 5 minutes each in 0.1M cacodylate buffer, pH 7.4.

10 Other Embodiments

Although the present invention has been described with reference to preferred embodiments, one skilled in the art can easily ascertain its essential characteristics and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to  
15 adapt it to various usages and conditions. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the present invention.

20 All publications and patents mentioned in this specification are hereby incorporated by reference.

What is claimed is:

### Claims

1. A method of determining whether a test subject has, or is at risk of developing, a titin-related disease or condition, said method comprising analyzing a nucleic acid molecule of a sample from the test subject to  
5 determine whether the test subject has a mutation in a *titin* gene, wherein the presence of said mutation is an indication that said test subject has, or is at risk of developing, a titin-related disease.
2. The method of claim 1, further comprising the step of using nucleic acid molecule primers specific for the *titin* gene for nucleic acid  
10 molecule amplification of the *titin* gene by the polymerase chain reaction.
3. The method of claim 1, further comprising the step of sequencing *titin* nucleic acid molecules from said test subject.
4. The method of claim 1, wherein said test subject is a mammal.
5. The method of claim 1, wherein said test subject is human.
- 15 6. The method of claim 1, wherein said disease or condition is heart failure.
7. The method of claim 1, wherein said mutation is the *pickwick* mutation.

8. A method for identifying a compound that can be used to treat or to prevent heart failure, said method comprising contacting an organism comprising a *titin* mutation and having a phenotype characteristic of heart failure with said compound, and determining the effect of said compound on said phenotype, wherein detection of an improvement in said phenotype indicates the identification of a compound that can be used to treat or to prevent heart failure.
9. The method of claim 8, wherein said organism is a zebrafish.
10. The method of claim 8, wherein said *titin* mutation is the *pickwick* mutation.
11. A method of treating or preventing heart failure in a patient, said method comprising administering to said patient a compound identified using the method of claim 8.
12. The method of claim 11, wherein said patient has a mutation in the *titin* gene.
13. The method of claim 12, wherein said mutation is the *pickwick* mutation.
14. A non-human animal comprising a mutation in a *titin* gene.
15. The non-human animal of claim 14, wherein the non-human animal is a zebrafish.

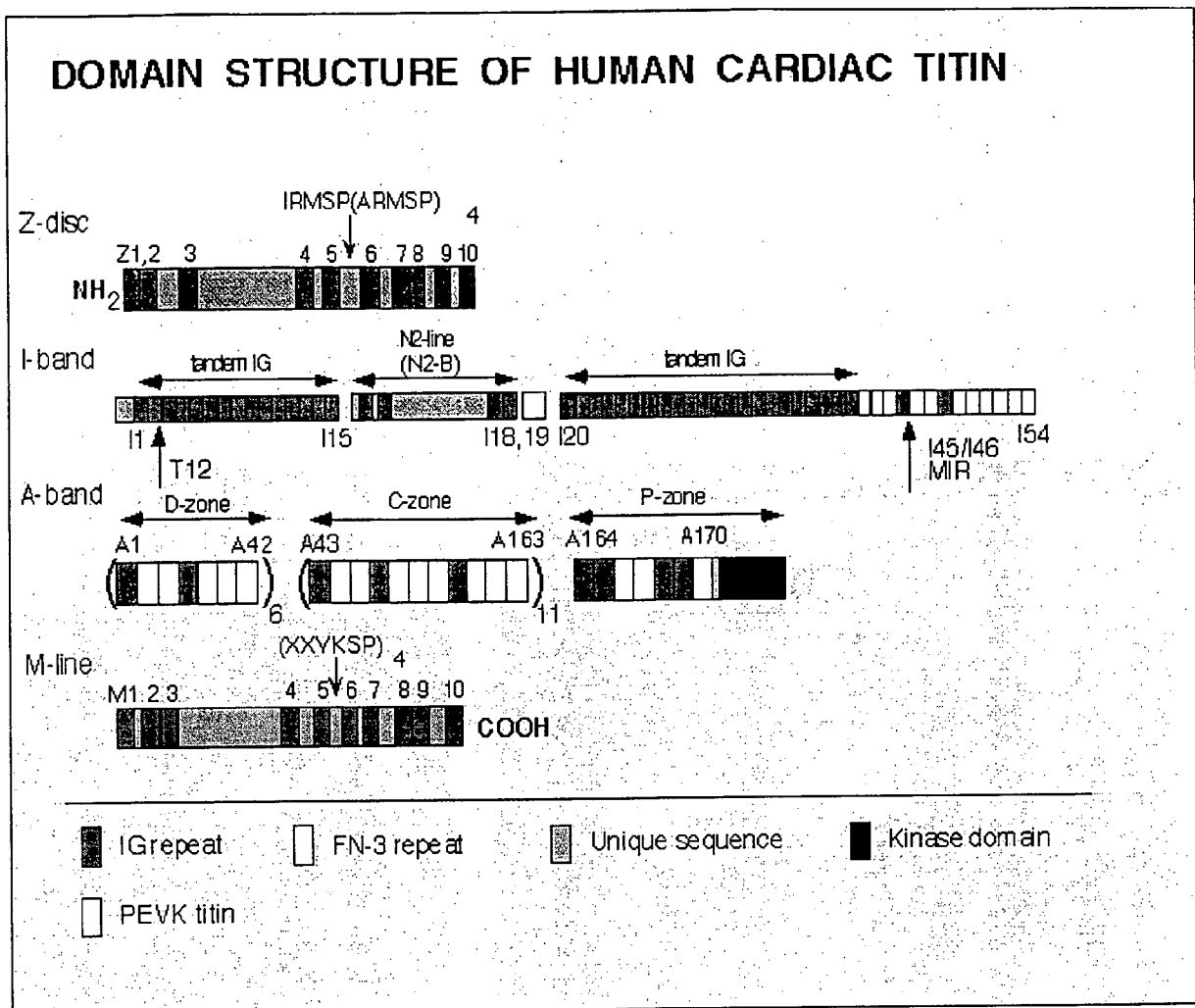


16. The non-human animal of claim 14, wherein the mutation is in a cardiac-specific exon of said *titin* gene.

17. The non-human animal of claim 16, wherein the mutation is in the N2B exon of said *titin* gene.

5        18. The non-human animal of claim 14, wherein the mutation results in the presence of a stop codon in said *titin* gene.

19. The non-human animal of claim 14, wherein the mutation is the *pickwick* mutation.



**Fig. 1 Domain structure of the titin filament.**

## SEQUENCE LISTING

&lt;110&gt; The General Hospital Corporation

<120> Methods for Diagnosing and Treating  
Heart Disease

&lt;130&gt; 00786/381W02

&lt;150&gt; US 60/175,787

&lt;151&gt; 2000-01-12

&lt;160&gt; 11

&lt;170&gt; FastSEQ for Windows Version 4.0

&lt;210&gt; 1

&lt;211&gt; 81940

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 1

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&lt;210&gt; 2

&lt;211&gt; 26926

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 2

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Met Thr Thr Gln Ala Pro Thr Phe Thr Gln Pro Leu Gln Ser Val Val
 1          5          10          15
Val Leu Glu Gly Ser Thr Ala Thr Phe Glu Ala His Ile Ser Gly Phe
 20          25          30
Pro Val Pro Glu Val Ser Trp Phe Arg Asp Gly Gln Val Ile Ser Thr
 35          40          45
Ser Thr Leu Pro Gly Val Gln Ile Ser Phe Ser Asp Gly Arg Ala Lys
 50          55          60
Leu Thr Ile Pro Ala Val Thr Lys Ala Asn Ser Gly Arg Tyr Ser Leu
 65          70          75          80
Lys Ala Thr Asn Gly Ser Gly Gln Ala Thr Ser Thr Ala Glu Leu Leu
 85          90          95
Val Lys Ala Glu Thr Ala Pro Pro Asn Phe Val Gln Arg Leu Gln Ser
100          105          110
Met Thr Val Arg Gln Gly Ser Gln Val Arg Leu Gln Val Arg Val Thr
115          120          125
Gly Ile Pro Thr Pro Val Val Lys Phe Tyr Arg Asp Gly Ala Glu Ile
130          135          140
Gln Ser Ser Leu Asp Phe Gln Ile Ser Gln Glu Gly Asp Leu Tyr Ser
145          150          155          160
Leu Leu Ile Ala Glu Ala Tyr Pro Glu Asp Ser Gly Thr Tyr Ser Val
165          170          175
Asn Ala Thr Asn Ser Val Gly Arg Ala Thr Ser Thr Ala Glu Leu Leu
180          185          190
Val Gln Gly Glu Glu Glu Val Pro Ala Lys Lys Thr Lys Thr Ile Val
195          200          205
Ser Thr Ala Gln Ile Ser Glu Ser Arg Gln Thr Arg Ile Glu Lys Lys
210          215          220

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Ile	Glu	Ala	His	Phe	Asp	Ala	Arg	Ser	Ile	Ala	Thr	Val	Glu	Met	Val
225					230					235					240
Ile	Asp	Gly	Ala	Ala	Gly	Gln	Gln	Leu	Pro	His	Lys	Thr	Pro	Pro	Arg
			245						250					255	
Ile	Pro	Pro	Lys	Pro	Lys	Ser	Arg	Ser	Pro	Thr	Pro	Pro	Ser	Ile	Ala
			260					265						270	
Ala	Lys	Ala	Gln	Leu	Ala	Arg	Gln	Gln	Ser	Pro	Ser	Pro	Ile	Arg	His
		275					280					285			
Ser	Pro	Ser	Pro	Val	Arg	His	Val	Arg	Ala	Pro	Thr	Pro	Ser	Pro	Val
	290				295						300				
Arg	Ser	Val	Ser	Pro	Ala	Ala	Arg	Ile	Ser	Thr	Ser	Pro	Ile	Arg	Ser
305				310						315					320
Val	Arg	Ser	Pro	Leu	Met	Arg	Lys	Thr	Gln	Ala	Ser	Thr	Val	Ala	
			325					330						335	
Thr	Gly	Pro	Glu	Val	Pro	Pro	Pro	Trp	Lys	Gln	Glu	Gly	Tyr	Val	Ala
		340						345					350		
Ser	Ser	Ser	Glu	Ala	Glu	Met	Arg	Glu	Thr	Thr	Leu	Thr	Thr	Ser	Thr
	355						360					365			
Gln	Ile	Arg	Thr	Glu	Glu	Arg	Trp	Glu	Gly	Arg	Tyr	Gly	Val	Gln	Glu
	370					375					380				
Gln	Val	Thr	Ile	Ser	Gly	Ala	Ala	Gly	Ala	Ala	Ser	Val	Ser	Ala	
385				390					395					400	
Ser	Ala	Ser	Tyr	Ala	Ala	Glu	Ala	Val	Ala	Thr	Gly	Ala	Lys	Glu	Val
			405						410					415	
Lys	Gln	Asp	Ala	Asp	Lys	Ser	Ala	Ala	Val	Ala	Thr	Val	Val	Ala	Ala
		420						425					430		
Val	Asp	Met	Ala	Arg	Val	Arg	Glu	Pro	Val	Ile	Ser	Ala	Val	Glu	Gln
	435						440						445		
Thr	Ala	Gln	Arg	Thr	Thr	Thr	Thr	Ala	Val	His	Ile	Gln	Pro	Ala	Gln
	450				455							460			
Glu	Gln	Val	Arg	Lys	Glu	Ala	Glu	Lys	Thr	Ala	Val	Thr	Lys	Val	Val
465				470					475						480
Val	Ala	Ala	Asp	Lys	Ala	Lys	Glu	Gln	Glu	Leu	Lys	Ser	Arg	Thr	Lys
			485						490					495	
Glu	Ile	Ile	Thr	Lys	Gln	Glu	Gln	Met	His	Val	Thr	His	Glu	Gln	
	500						505					510			
Ile	Arg	Lys	Glu	Thr	Glu	Lys	Thr	Phe	Val	Pro	Lys	Val	Val	Ile	Ser
	515						520					525			
Ala	Ala	Lys	Ala	Lys	Glu	Gln	Glu	Thr	Arg	Ile	Ser	Glu	Glu	Ile	Thr
	530				535					540					
Lys	Lys	Gln	Lys	Gln	Val	Thr	Gln	Glu	Ala	Ile	Met	Lys	Glu	Thr	Arg
545				550					555						560
Lys	Thr	Val	Val	Pro	Lys	Val	Ile	Val	Ala	Thr	Pro	Lys	Val	Lys	Glu
			565						570					575	
Gln	Asp	Leu	Val	Ser	Arg	Gly	Arg	Glu	Gly	Ile	Thr	Thr	Lys	Arg	Glu
	580						585						590		
Gln	Val	Gln	Ile	Thr	Gln	Glu	Lys	Met	Arg	Lys	Glu	Ala	Glu	Lys	Thr
	595						600					605			
Ala	Leu	Ser	Thr	Ile	Ala	Val	Ala	Thr	Ala	Lys	Ala	Lys	Glu	Gln	Glu
	610				615						620				
Thr	Ile	Leu	Arg	Thr	Arg	Glu	Thr	Met	Ala	Thr	Arg	Gln	Glu	Gln	Ile
625				630					635						640
Gln	Val	Thr	His	Gly	Lys	Val	Asp	Val	Gly	Lys	Lys	Ala	Glu	Ala	Val
			645						650					655	
Ala	Thr	Val	Val	Ala	Ala	Val	Asp	Gln	Ala	Arg	Val	Arg	Glu	Pro	Arg
		660					665						670		
Glu	Pro	Gly	His	Leu	Glu	Glu	Ser	Tyr	Ala	Gln	Gln	Thr	Thr	Leu	Glu
	675						680					685			
Tyr	Gly	Tyr	Lys	Glu	Arg	Ile	Ser	Ala	Ala	Lys	Val	Ala	Glu	Pro	Pro
	690					695					700				
Gln	Arg	Pro	Ala	Ser	Glu	Pro	His	Val	Val	Pro	Lys	Ala	Val	Lys	Pro
705				710						715					720

Arg	Val	Ile	Gln	Ala	Pro	Ser	Glu	Thr	His	Ile	Lys	Thr	Thr	Asp	Gln	725	730	735
Lys	Gly	Met	His	Ile	Ser	Ser	Gln	Ile	Lys	Lys	Thr	Thr	Asp	Leu	Thr	740	745	750
Thr	Glu	Arg	Leu	Val	His	Val	Asp	Lys	Arg	Pro	Arg	Thr	Ala	Ser	Pro	755	760	765
His	Phe	Thr	Val	Ser	Lys	Ile	Ser	Val	Pro	Lys	Thr	Glu	His	Gly	Tyr	770	775	780
Glu	Ala	Ser	Ile	Ala	Gly	Ser	Ala	Ile	Ala	Thr	Leu	Gln	Lys	Glu	Leu	785	790	795
Ser	Ala	Thr	Ser	Ser	Ala	Gln	Lys	Ile	Thr	Lys	Ser	Val	Lys	Ala	Pro	805	810	815
Thr	Val	Lys	Pro	Ser	Glu	Thr	Arg	Val	Arg	Ala	Glu	Pro	Thr	Pro	Leu	820	825	830
Pro	Gln	Phe	Pro	Phe	Ala	Asp	Thr	Pro	Asp	Thr	Tyr	Lys	Ser	Glu	Ala	835	840	845
Gly	Val	Glu	Val	Lys	Lys	Glu	Val	Gly	Val	Ser	Ile	Thr	Gly	Thr	Thr	850	855	860
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Thr	Glu	Thr	Ala	Arg	Val	Pro	Ala	Pro	Val	Glu	Ile	Pro	Val	Thr	Pro	885	890	895
Pro	Thr	Leu	Val	Ser	Gly	Leu	Lys	Asn	Val	Thr	Val	Ile	Glu	Gly	Glu	900	905	910
Ser	Val	Thr	Leu	Glu	Cys	His	Ile	Ser	Gly	Tyr	Pro	Ser	Pro	Thr	Val	915	920	925
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Arg	Phe	Val	Glu	Ser	Arg	Asp	Val	Val	Met	Thr	Asp	Thr	Ser	Leu	Thr	1010	1015	1020
Glu	Glu	Gln	Ala	Gly	Pro	Gly	Glu	Pro	Ala	Ala	Pro	Tyr	Phe	Ile	Thr	1025	1030	1035
Lys	Pro	Val	Val	Gln	Lys	Leu	Val	Glu	Gly	Gly	Ser	Val	Val	Phe	Gly	1045	1050	1055
Cys	Gln	Val	Gly	Gly	Asn	Pro	Lys	Pro	His	Val	Tyr	Trp	Lys	Lys	Ser	1060	1065	1070
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Ala	Gly	Glu	Tyr	Thr	Ile	Val	Val	Arg	Asn	Lys	His	Gly	Glu	Thr	Ser	1105	1110	1115
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Glu	Pro	Glu	Val	Gly	Glu	Thr	Ala	Pro	Gly	Phe	Val	Tyr	Ser	Glu	Tyr	1155	1160	1165
Glu	Lys	Glu	Tyr	Glu	Lys	Glu	Gln	Ala	Leu	Ile	Arg	Lys	Lys	Met	Ala	1170	1175	1180
Lys	Asp	Thr	Val	Val	Val	Arg	Thr	Tyr	Val	Glu	Asp	Gln	Glu	Phe	His	1185	1190	1195
Ile	Ser	Ser	Phe	Glu	Glu	Arg	Leu	Ile	Lys	Glu	Ile	Glu	Tyr	Arg	Ile	1205	1210	1215

Ile Lys Thr Thr Leu Glu Glu Leu Leu Glu Glu Asp Gly Glu Glu Lys  
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 Met Ala Val Asp Ile Ser Glu Ser Glu Ala Val Glu Ser Gly Phe Asp  
 1235 1240 1245  
 Leu Arg Ile Lys Asn Tyr Arg Ile Leu Glu Gly Met Gly Val Thr Phe  
 1250 1255 1260  
 His Cys Lys Met Ser Gly Tyr Pro Leu Pro Lys Ile Ala Trp Tyr Lys  
 1265 1270 1275 1280  
 Asp Gly Lys Arg Ile Lys His Gly Glu Arg Tyr Gln Met Asp Phe Leu  
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 Gln Asp Gly Arg Ala Ser Leu Arg Ile Pro Val Val Leu Pro Glu Asp  
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 Leu Lys Ile Asp Ser Thr Val Ser Gln Asp Ser Ala Trp Tyr Thr Ala  
 1570 1575 1580  
 Thr Ala Ile Asn Lys Ala Gly Arg Asp Thr Thr Arg Cys Lys Val Asn  
 1585 1590 1595 1600  
 Val Glu Val Glu Phe Ala Glu Pro Glu Pro Glu Arg Lys Leu Ile Ile  
 1605 1610 1615  
 Pro Arg Gly Thr Tyr Arg Ala Lys Glu Ile Ala Ala Pro Glu Leu Glu  
 1620 1625 1630  
 Pro Leu His Leu Arg Tyr Gly Gln Glu Gln Trp Glu Glu Gly Asp Leu  
 1635 1640 1645  
 Tyr Asp Lys Glu Lys Gln Gln Lys Pro Phe Phe Lys Lys Lys Leu Thr  
 1650 1655 1660  
 Ser Leu Arg Leu Lys Arg Phe Gly Pro Ala His Phe Glu Cys Arg Leu  
 1665 1670 1675 1680  
 Thr Pro Ile Ser Asp Pro Thr Met Val Val Glu Trp Leu His Asp Gly  
 1685 1690 1695  
 Lys Pro Leu Glu Ala Ala Asn Arg Leu Arg Met Ile Asn Glu Phe Gly  
 1700 1705 1710

Tyr Cys Ser Leu Asp Tyr Gly Val Ala Tyr Ser Arg Asp Ser Gly Ile  
 1715 1720 1725  
 Ile Thr Cys Arg Ala Thr Asn Lys Tyr Gly Thr Asp His Thr Ser Ala  
 1730 1735 1740  
 Thr Leu Ile Val Lys Asp Glu Lys Ser Leu Val Glu Glu Ser Gln Leu  
 1745 1750 1755 1760  
 Pro Glu Gly Arg Lys Gly Leu Gln Arg Ile Glu Glu Leu Glu Arg Met  
 1765 1770 1775  
 Ala His Glu Gly Ala Leu Thr Gly Val Thr Thr Asp Gln Lys Glu Lys  
 1780 1785 1790  
 Gln Lys Pro Asp Ile Val Leu Tyr Pro Glu Pro Val Arg Val Leu Glu  
 1795 1800 1805  
 Gly Glu Thr Ala Arg Phe Arg Cys Arg Val Thr Gly Tyr Pro Gln Pro  
 1810 1815 1820  
 Lys Val Asn Trp Tyr Leu Asn Gly Gln Leu Ile Arg Lys Ser Lys Arg  
 1825 1830 1835 1840  
 Phe Arg Val Arg Tyr Asp Gly Ile His Tyr Leu Asp Ile Val Asp Cys  
 1845 1850 1855  
 Lys Ser Tyr Asp Thr Gly Glu Val Lys Val Thr Ala Glu Asn Pro Glu  
 1860 1865 1870  
 Gly Val Ile Glu His Lys Val Lys Leu Glu Ile Gln Gln Arg Glu Asp  
 1875 1880 1885  
 Phe Arg Ser Val Leu Arg Arg Ala Pro Glu Pro Arg Pro Glu Phe His  
 1890 1895 1900  
 Val His Glu Pro Gly Lys Leu Gln Phe Glu Val Gln Lys Val Asp Arg  
 1905 1910 1915 1920  
 Pro Val Asp Thr Thr Glu Thr Lys Glu Val Val Lys Leu Lys Arg Ala  
 1925 1930 1935  
 Glu Arg Ile Thr His Glu Lys Val Pro Glu Glu Ser Glu Glu Leu Arg  
 1940 1945 1950  
 Ser Lys Phe Lys Arg Arg Thr Glu Glu Gly Tyr Tyr Glu Ala Ile Thr  
 1955 1960 1965  
 Ala Val Glu Leu Lys Ser Arg Lys Lys Asp Glu Ser Tyr Glu Glu Leu  
 1970 1975 1980  
 Leu Arg Lys Thr Lys Asp Glu Leu Leu His Trp Thr Lys Glu Leu Thr  
 1985 1990 1995 2000  
 Glu Glu Glu Lys Lys Ala Leu Ala Glu Glu Gly Lys Ile Thr Ile Pro  
 2005 2010 2015  
 Thr Phe Lys Pro Asp Lys Ile Glu Leu Ser Pro Ser Met Glu Ala Pro  
 2020 2025 2030  
 Lys Ile Phe Glu Arg Ile Gln Ser Gln Thr Val Gly Gln Gly Ser Asp  
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 Ala His Phe Arg Val Arg Val Val Gly Lys Pro Asp Pro Glu Cys Glu  
 2050 2055 2060  
 Trp Tyr Lys Asn Gly Val Lys Ile Glu Arg Ser Asp Arg Ile Tyr Trp  
 2065 2070 2075 2080  
 Tyr Trp Pro Glu Asp Asn Val Cys Glu Leu Val Ile Arg Asp Val Thr  
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 Ala Glu Asp Ser Ala Ser Ile Met Val Lys Ala Ile Asn Ile Ala Gly  
 2100 2105 2110  
 Glu Thr Ser Ser His Ala Phe Leu Leu Val Gln Ala Lys Gln Leu Ile  
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 Thr Phe Thr Gln Glu Leu Gln Asp Val Val Ala Lys Glu Lys Asp Thr  
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 Met Ala Thr Phe Glu Cys Glu Thr Ser Glu Pro Phe Val Lys Val Lys  
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 Trp Tyr Lys Asp Gly Met Glu Val His Glu Gly Asp Lys Tyr Arg Met  
 2165 2170 2175  
 His Ser Asp Arg Lys Val His Phe Leu Ser Ile Leu Thr Ile Asp Thr  
 2180 2185 2190  
 Ser Asp Ala Glu Asp Tyr Ser Cys Val Leu Val Glu Asp Glu Asn Val  
 2195 2200 2205

Lys Thr Thr Ala Lys Leu Ile Val Glu Gly Ala Val Val Glu Phe Val  
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 Lys Glu Leu Gln Asp Ile Glu Val Pro Glu Ser Tyr Ser Gly Glu Leu  
 2225 2230 2235 2240  
 Glu Cys Ile Val Ser Pro Glu Asn Ile Glu Gly Lys Trp Tyr His Asn  
 2245 2250 2255  
 Asp Val Glu Leu Lys Ser Asn Gly Lys Tyr Thr Ile Thr Ser Arg Arg  
 2260 2265 2270  
 Gly Arg Gln Asn Leu Thr Val Lys Asp Val Thr Lys Glu Asp Gln Gly  
 2275 2280 2285  
 Glu Tyr Ser Phe Val Ile Asp Gly Lys Lys Thr Thr Cys Lys Leu Lys  
 2290 2295 2300  
 Met Lys Pro Arg Pro Ile Ala Ile Leu Gln Gly Leu Ser Asp Gln Lys  
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 Val Cys Glu Gly Asp Ile Val Gln Leu Glu Val Lys Val Ser Leu Glu  
 2325 2330 2335  
 Ser Val Glu Gly Val Trp Met Lys Asp Gly Gln Glu Val Gln Pro Ser  
 2340 2345 2350  
 Asp Arg Val His Ile Val Ile Asp Lys Gln Ser His Met Leu Leu Ile  
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 Glu Asp Met Thr Lys Glu Asp Ala Gly Asn Tyr Ser Phe Thr Ile Pro  
 2370 2375 2380  
 Ala Leu Gly Leu Ser Thr Ser Gly Arg Val Ser Val Tyr Ser Val Asp  
 2385 2390 2395 2400  
 Val Ile Thr Pro Leu Lys Asp Val Asn Val Ile Glu Gly Thr Lys Ala  
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 Val Leu Glu Cys Lys Val Ser Val Pro Asp Val Thr Ser Val Lys Trp  
 2420 2425 2430  
 Tyr Leu Asn Asp Glu Gln Ile Lys Pro Asp Asp Arg Val Gln Ala Ile  
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 Val Lys Gly Thr Lys Gln Arg Leu Val Ile Asn Arg Thr His Ala Ser  
 2450 2455 2460  
 Asp Glu Gly Pro Tyr Lys Leu Ile Val Gly Arg Val Glu Thr Asn Cys  
 2465 2470 2475 2480  
 Asn Leu Ser Val Glu Lys Ile Lys Ile Ile Arg Gly Leu Arg Asp Leu  
 2485 2490 2495  
 Thr Cys Thr Glu Thr Gln Asn Val Val Phe Glu Val Glu Leu Ser His  
 2500 2505 2510  
 Ser Gly Ile Asp Val Leu Trp Asn Phe Lys Asp Lys Glu Ile Lys Pro  
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 Ser Ser Lys Tyr Lys Ile Glu Ala His Gly Lys Ile Tyr Lys Leu Thr  
 2530 2535 2540  
 Val Leu Asn Met Met Lys Asp Asp Glu Gly Lys Tyr Thr Phe Tyr Ala  
 2545 2550 2555 2560  
 Gly Glu Asn Met Thr Ser Gly Lys Leu Thr Val Ala Gly Gly Ala Ile  
 2565 2570 2575  
 Ser Lys Pro Leu Thr Asp Gln Thr Val Ala Glu Ser Gln Glu Ala Val  
 2580 2585 2590  
 Phe Glu Cys Glu Val Ala Asn Pro Asp Ser Lys Gly Glu Trp Leu Arg  
 2595 2600 2605  
 Asp Gly Lys His Leu Pro Leu Thr Asn Asn Ile Arg Ser Glu Ser Asp  
 2610 2615 2620  
 Gly His Lys Arg Arg Leu Ile Ile Ala Ala Thr Lys Leu Asp Asp Ile  
 2625 2630 2635 2640  
 Gly Glu Tyr Thr Tyr Lys Val Ala Thr Ser Lys Thr Ser Ala Lys Leu  
 2645 2650 2655  
 Lys Val Glu Ala Val Lys Ile Lys Lys Thr Leu Lys Asn Leu Thr Val  
 2660 2665 2670  
 Thr Glu Thr Gln Asp Ala Val Phe Thr Val Glu Leu Thr His Pro Asn  
 2675 2680 2685  
 Val Lys Gly Val Gln Trp Ile Lys Asn Gly Val Val Leu Glu Ser Asn  
 2690 2695 2700

Glu Lys Tyr Ala Ile Ser Val Lys Gly Thr Ile Tyr Ser Leu Arg Ile  
 2705 2710 2715 2720  
 Lys Asn Cys Ala Ile Val Asp Glu Ser Val Tyr Gly Phe Arg Leu Gly  
 2725 2730 2735  
 Arg Leu Gly Ala Ser Ala Arg Leu His Val Glu Thr Val Lys Ile Ile  
 2740 2745 2750  
 Lys Lys Pro Lys Asp Val Thr Ala Leu Glu Asn Ala Thr Val Ala Phe  
 2755 2760 2765  
 Glu Val Ser Val Ser His Asp Thr Val Pro Val Lys Trp Phe His Lys  
 2770 2775 2780  
 Ser Val Glu Ile Lys Pro Ser Asp Lys His Arg Leu Val Ser Glu Arg  
 2785 2790 2795 2800  
 Lys Val His Lys Leu Met Leu Gln Asn Ile Ser Pro Ser Asp Ala Gly  
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 Glu Tyr Thr Ala Val Val Gly Gln Leu Glu Cys Lys Ala Lys Leu Phe  
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 Val Glu Thr Leu His Ile Thr Lys Thr Met Lys Asn Ile Glu Val Pro  
 2835 2840 2845  
 Glu Thr Lys Thr Ala Ser Phe Glu Cys Glu Val Ser His Phe Asn Val  
 2850 2855 2860  
 Pro Ser Met Trp Leu Lys Asn Gly Val Glu Ile Glu Met Ser Glu Lys  
 2865 2870 2875 2880  
 Phe Lys Ile Val Val Gln Gly Lys Leu His Gln Leu Ile Ile Met Asn  
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 2930 2935 2940  
 Thr Val Asn Tyr Glu Gly Ile Ser Tyr Lys Trp Leu Lys Asn Gly Val  
 2945 2950 2955 2960  
 Glu Ile Lys Ser Thr Asp Lys Cys Gln Met Arg Thr Lys Lys Leu Thr  
 2965 2970 2975  
 His Ser Leu Asn Ile Arg Asn Val His Phe Gly Asp Ala Ala Asp Tyr  
 2980 2985 2990  
 Thr Phe Val Ala Gly Lys Ala Thr Ser Thr Ala Thr Leu Tyr Val Glu  
 2995 3000 3005  
 Ala Arg His Ile Glu Phe Arg Lys His Ile Lys Asp Ile Lys Val Leu  
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 Glu Lys Lys Arg Ala Met Phe Glu Cys Glu Val Ser Glu Pro Asp Ile  
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 Thr Val Gln Trp Met Lys Asp Asp Gln Glu Leu Gln Ile Thr Asp Arg  
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 Ile Lys Ile Gln Lys Glu Lys Tyr Val His Arg Leu Leu Ile Pro Ser  
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 Thr Arg Met Ser Asp Ala Gly Lys Tyr Thr Val Val Ala Gly Gly Asn  
 3075 3080 3085  
 Val Ser Thr Ala Lys Leu Phe Val Glu Gly Arg Asp Val Arg Ile Arg  
 3090 3095 3100  
 Ser Ile Lys Lys Glu Val Gln Val Ile Glu Lys Gln Arg Ala Val Val  
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 Glu Phe Glu Val Asn Glu Asp Asp Val Asp Ala His Trp Tyr Lys Asp  
 3125 3130 3135  
 Gly Ile Glu Ile Asn Phe Gln Val Gln Glu Arg His Lys Tyr Val Val  
 3140 3145 3150  
 Glu Arg Arg Ile His Arg Met Phe Ile Ser Glu Thr Arg Gln Ser Asp  
 3155 3160 3165  
 Ala Gly Glu Tyr Thr Phe Val Ala Gly Arg Asn Arg Ser Ser Val Thr  
 3170 3175 3180  
 Leu Tyr Val Asn Ala Pro Glu Pro Pro Gln Val Leu Gln Glu Leu Gln  
 3185 3190 3195 3200

Pro Val Thr Val Gln Ser Gly Lys Pro Ala Arg Phe Cys Ala Met Ile  
 3205 3210 3215  
 Ser Gly Arg Pro Gln Pro Lys Ile Ser Trp Tyr Lys Glu Glu Gln Leu  
 3220 3225 3230  
 Leu Ser Thr Gly Phe Lys Cys Lys Phe Leu His Asp Gly Gln Glu Tyr  
 3235 3240 3245  
 Thr Leu Leu Leu Ile Glu Ala Phe Pro Glu Asp Ala Ala Val Tyr Thr  
 3250 3255 3260  
 Cys Glu Ala Lys Asn Asp Tyr Gly Val Ala Thr Thr Ser Ala Ser Leu  
 3265 3270 3275 3280  
 Ser Val Glu Val Pro Glu Val Val Ser Pro Asp Gln Glu Met Pro Val  
 3285 3290 3295  
 Tyr Pro Pro Ala Ile Ile Thr Pro Leu Gln Asp Thr Val Thr Ser Glu  
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 Gly Gln Pro Ala Arg Phe Gln Cys Arg Val Ser Gly Thr Asp Leu Lys  
 3315 3320 3325  
 Val Ser Trp Tyr Ser Lys Asp Lys Lys Ile Lys Pro Ser Arg Phe Phe  
 3330 3335 3340  
 Arg Met Thr Gln Phe Glu Asp Thr Tyr Gln Leu Glu Ile Ala Glu Ala  
 3345 3350 3355 3360  
 Tyr Pro Glu Asp Glu Gly Thr Tyr Thr Phe Val Ala Asn Asn Ala Val  
 3365 3370 3375  
 Gly Gln Val Ser Ser Thr Ala Asn Leu Ser Leu Glu Ala Pro Glu Ser  
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 Ile Leu His Glu Arg Ile Glu Gln Glu Ile Glu Met Glu Met Lys Glu  
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 Phe Ser Ser Ser Phe Leu Ser Ala Glu Glu Glu Gly Leu His Ser Ala  
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 Ser Pro Val Tyr Pro Thr Lys Phe Asp Ser Glu Lys Glu Gly Thr Gly  
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 Pro Ile Phe Ile Lys Glu Val Ser Asn Ala Asp Ile Ser Met Gly Asp  
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 Val Ala Thr Leu Ser Val Thr Val Ile Gly Ile Pro Lys Pro Lys Ile  
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 Gln Trp Phe Phe Asn Gly Val Leu Leu Thr Pro Ser Ala Asp Tyr Lys  
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 Phe Val Phe Asp Gly Asp Asp His Ser Leu Ile Ile Leu Phe Thr Lys  
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 Leu Glu Asp Glu Gly Glu Tyr Thr Cys Met Ala Ser Asn Asp Tyr Gly  
 3525 3530 3535  
 Lys Thr Ile Cys Ser Ala Tyr Leu Lys Ile Asn Ser Lys Gly Glu Gly  
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 His Lys Asp Thr Glu Thr Glu Ser Ala Val Ala Lys Ser Leu Glu Lys  
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 Leu Gly Gly Pro Cys Pro Pro His Phe Leu Lys Glu Leu Lys Pro Ile  
 3570 3575 3580  
 Arg Cys Ala Gln Gly Leu Pro Ala Ile Phe Glu Tyr Thr Val Val Gly  
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 Glu Pro Ala Pro Thr Val Thr Trp Phe Lys Glu Asn Lys Gln Leu Cys  
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 Thr Ser Val Tyr Tyr Thr Ile Ile His Asn Pro Asn Gly Ser Gly Thr  
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 Phe Ile Val Asn Asp Pro Gln Arg Glu Asp Ser Gly Leu Tyr Ile Cys  
 3635 3640 3645  
 Lys Ala Glu Asn Met Leu Gly Glu Ser Thr Cys Ala Ala Glu Leu Leu  
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 Val Leu Leu Glu Asp Thr Asp Met Thr Asp Thr Pro Cys Lys Ala Lys  
 3665 3670 3675 3680  
 Ser Thr Pro Glu Ala Pro Glu Asp Phe Pro Gln Thr Pro Leu Lys Gly  
 3685 3690 3695



Pro Ala Val Glu Ala Leu Asp Ser Glu Gln Glu Ile Ala Thr Phe Val  
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 Lys Asp Thr Ile Leu Lys Ala Ala Leu Ile Thr Glu Glu Asn Gln Gln  
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 Leu Ser Tyr Glu His Ile Ala Lys Ala Asn Glu Leu Ser Ser Gln Leu  
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 Pro Leu Gly Ala Gln Glu Leu Gln Ser Ile Leu Glu Gln Asp Lys Leu  
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 Thr Pro Glu Ser Thr Arg Glu Phe Leu Cys Ile Asn Gly Ser Ile His  
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 Gln Ser Gln Lys Thr Phe Ser Lys Glu Gly Ile Leu Met Pro Glu Glu  
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 Pro Pro Met His Ser Tyr Leu Thr Ser Val Ala Glu Glu Val Leu Ser  
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 Leu Gln Lys Gln Glu Ala Gln Ser Ala Leu Ile Leu Ser Gln Ser Leu  
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 Gly Gly Lys Ile Leu Ile Glu Ser Ala Asn Pro Leu Glu Asn Ala Gly  
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 Asn Val Val Met Pro Pro Asp Gln Ile Ile Glu Ser Lys Arg Glu Pro  
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 Val Ala Ile Lys Lys Val Gln Glu Val Gln Gly Arg Asp Leu Leu Ser  
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 Lys Glu Ser Leu Leu Ser Gly Ile Pro Glu Glu Gln Arg Leu Asn Leu  
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 Lys Ile Gln Ile Cys Arg Ala Leu Gln Ala Ala Val Ala Ser Glu Gln  
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 Pro Gly Leu Phe Ser Glu Trp Leu Arg Asn Ile Glu Lys Val Glu Val  
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 Glu Ala Val Asn Ile Thr Gln Glu Pro Arg His Ile Met Cys Met Tyr  
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 Glu Asp Val Asp Pro Gln Met Ala Asn Leu Lys Met Glu Leu Arg Asp  
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 Gly Pro Arg Ile Gln Gln Gly Ala Lys Thr Ser Leu Gln Glu Glu Met  
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 Asp Ser Phe Ser Gly Ser Gln Lys Val Glu Pro Ile Thr Glu Pro Glu  
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 Val Glu Ser Lys Tyr Leu Ile Ser Thr Glu Glu Val Ser Tyr Phe Asn  
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 Val Gln Ser Arg Val Lys Tyr Leu Asp Ala Thr Pro Val Thr Lys Gly  
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Val Ala Ser Ala Val Val Ser Asp Glu Lys Gln Asp Glu Ser Leu Lys  
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 Pro Ser Glu Glu Lys Glu Glu Ser Ser Ser Glu Ser Gly Thr Glu Glu  
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 Val Ala Thr Val Lys Ile Gln Glu Ala Glu Gly Gly Leu Ile Lys Glu  
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 Gly Asp Ile Val His Leu Thr Thr Ser Ile Thr Asn Ala Lys Glu Val  
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 Asn Trp Tyr Phe Glu Asn Lys Leu Val Pro Ser Asp Glu Lys Phe Lys  
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 Cys Leu Gln Asp Gln Asn Thr Tyr Thr Leu Val Ile Asp Lys Val Asn  
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 Thr Glu Asp His Gln Gly Glu Tyr Val Cys Glu Ala Leu Asn Asp Ser  
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 Pro Val Ile Lys Arg Lys Ile Glu Pro Leu Glu Val Ala Leu Gly His  
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 Val Val Asp Cys Gly Glu Tyr Thr Cys Lys Ala Ser Asn Glu Tyr Gly  
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 Lys Lys Val Arg Lys Leu Leu Pro Glu Arg Lys Pro Glu Pro Lys Glu  
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 Lys Gly Val Pro Lys Lys Thr Pro Ser Pro Ile Glu Ala Glu Arg Arg  
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 Lys Leu Arg Pro Gly Ser Gly Gly Glu Lys Pro Pro Asp Glu Ala Pro  
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Gly Glu Tyr Thr Cys Val Leu Arg Leu Gly Asn Lys Glu Lys Thr Ser  
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 Cys Glu Leu Asn Lys Glu Arg Asp Val Val Trp Arg Lys Asp Gly Lys  
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 Ile Val Val Glu Lys Pro Gly Arg Ile Val Pro Gly Val Ile Gly Leu  
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 Tyr Thr Val Thr Val Glu Asn Ala Asn Asn Leu Glu Cys Ser Ser Cys  
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 Cys Glu Ile Lys Ala Glu Gly Gly Lys Arg Phe Leu Thr Leu His Lys  
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 Lys His Ile Leu Val Ile Asn Asp Ser Gln Phe Asp Asp Glu Gly Val  
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 Lys Glu Gly Glu Thr Ala Thr Phe Val Cys Glu Leu Ser His Glu Lys  
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 Met His Val Val Trp Phe Lys Asn Asp Ala Lys Leu His Thr Ser Arg  
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 Glu Val Thr Leu Asp Asp Ile Ser Gln Ile Lys Ala Gln Val Lys Glu  
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 Leu Ser Ser Thr Ala Gln Leu Lys Val Leu Glu Ala Asp Pro Tyr Phe  
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 Thr Val Lys Leu His Asp Lys Thr Ala Val Glu Lys Asp Glu Ile Thr  
 5170 5175 5180

Leu Lys Cys Glu Val Ser Lys Asp Val Pro Val Lys Trp Phe Lys Asp  
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 Gly Glu Glu Ile Val Pro Ser Pro Lys Tyr Ser Ile Lys Ala Asp Gly  
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 Glu Tyr Val Cys Asp Cys Gly Thr Asp Lys Thr Lys Ala Asn Val Thr  
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 Asp Val His Gly Gln Trp Lys Leu Lys Gly Gln Pro Leu Thr Ala Ser  
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 Pro Asp Cys Glu Ile Ile Glu Asp Gly Lys Lys His Ile Leu Ile Leu  
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 Lys Gly Thr Gln Glu Ile Thr Gly Asp Asp Arg Phe Glu Leu Ile Lys  
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 His Asp Asn Ile Arg Val Lys Trp Phe Lys Asn Asp Gln Arg Leu His  
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 Thr Phe Lys Asp Leu Ser Ile Asp Asp Thr Ser Gln Ile Arg Val Glu  
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 Pro Tyr Phe Thr Gly Lys Leu Gln Asp Tyr Thr Gly Val Glu Lys Asp  
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 Glu Val Ile Leu Gln Cys Glu Ile Ser Lys Ala Asp Ala Pro Val Lys  
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 Trp Phe Lys Asp Gly Lys Glu Ile Lys Pro Ser Lys Asn Ala Val Ile  
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 Lys Thr Asp Gly Lys Lys Arg Met Leu Ile Leu Lys Lys Ala Leu Lys  
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 Ser Asp Ile Gly Gln Tyr Thr Cys Asp Cys Gly Thr Asp Lys Thr Ser  
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 Gly Lys Leu Asp Ile Glu Asp Arg Glu Ile Lys Leu Val Arg Pro Leu  
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 His Ser Val Glu Val Met Glu Thr Glu Thr Ala Arg Phe Glu Thr Glu  
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 Ile Ser Glu Asp Asp Ile His Ala Asn Trp Lys Leu Lys Gly Glu Ala  
 5635 5640 5645  
 Leu Leu Gln Thr Pro Asp Cys Glu Ile Lys Glu Glu Gly Lys Ile His  
 5650 5655 5660  
 Ser Leu Val Leu His Asn Cys Arg Leu Asp Gln Thr Gly Gly Val Asp  
 5665 5670 5675 5680

Phe Gln Ala Ala Asn Val Lys Ser Ser Ala His Leu Arg Val Lys Pro  
 5685 5690 5695  
 Arg Val Ile Gly Leu Leu Arg Pro Leu Lys Asp Val Thr Val Thr Ala  
 5700 5705 5710  
 Gly Glu Thr Ala Thr Phe Asp Cys Glu Leu Ser Tyr Glu Asp Ile Pro  
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 Val Glu Trp Tyr Leu Lys Gly Lys Lys Leu Glu Pro Ser Asp Lys Val  
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 Val Pro Arg Ser Glu Gly Lys Val His Thr Leu Thr Leu Arg Asp Val  
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 Lys Leu Glu Asp Ala Gly Glu Val Gln Leu Thr Ala Lys Asp Phe Lys  
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 Thr His Ala Asn Leu Phe Val Lys Glu Pro Pro Val Glu Phe Thr Lys  
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 Pro Leu Glu Asp Gln Thr Val Glu Glu Gly Ala Thr Ala Val Leu Glu  
 5795 5800 5805  
 Cys Glu Val Ser Arg Glu Asn Ala Lys Val Lys Trp Phe Lys Asn Gly  
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 Thr Glu Ile Leu Lys Ser Lys Lys Tyr Glu Ile Val Ala Asp Gly Arg  
 5825 5830 5835 5840  
 Val Arg Lys Leu Val Ile His Asp Cys Thr Pro Glu Asp Ile Lys Thr  
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 Tyr Thr Cys Asp Ala Lys Asp Phe Lys Thr Ser Cys Asn Leu Asn Val  
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 Val Pro Pro His Val Glu Phe Leu Arg Pro Leu Thr Asp Leu Gln Val  
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 Arg Glu Lys Glu Met Ala Arg Phe Glu Cys Glu Leu Ser Arg Glu Asn  
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 Ala Lys Val Lys Trp Phe Lys Asp Gly Ala Glu Ile Lys Lys Gly Lys  
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 Lys Tyr Asp Ile Ile Ser Lys Gly Ala Val Arg Ile Leu Val Ile Asn  
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 Lys Cys Leu Leu Asp Asp Glu Ala Glu Tyr Ser Cys Glu Val Arg Thr  
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 Ala Arg Thr Ser Gly Met Leu Thr Val Leu Glu Glu Glu Ala Val Phe  
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 Thr Lys Asn Leu Ala Asn Ile Glu Val Ser Glu Thr Asp Thr Ile Lys  
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 Leu Val Cys Glu Val Ser Lys Pro Gly Ala Glu Val Ile Trp Tyr Lys  
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 Lys Val His Glu Leu Ala Ala Glu Phe Ile Ser Lys Pro Gln Asn Leu  
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 Ile Val Val Pro Leu Lys Asp Thr Arg Val Lys Glu Gln Gln Glu Val  
 6145 6150 6155 6160  
 Val Phe Asn Cys Glu Val Asn Thr Glu Gly Ala Lys Ala Lys Trp Phe  
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Arg Asn Glu Glu Ala Ile Phe Asp Ser Ser Lys Tyr Ile Ile Leu Gln  
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 Lys Asp Leu Val Tyr Thr Leu Arg Ile Arg Asp Ala His Leu Asp Asp  
 6195 6200 6205  
 Gln Ala Asn Tyr Asn Val Ser Leu Thr Asn His Arg Gly Glu Asn Val  
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 Lys Ser Ala Ala Asn Leu Ile Val Glu Glu Glu Asp Leu Arg Ile Val  
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 Glu Tyr Ile Val Thr Ala Gly Gln Asp Lys Ser Val Ala Glu Leu Leu  
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 Ile Ile Glu Ala Pro Thr Glu Phe Val Glu His Leu Glu Asp Gln Thr  
 6325 6330 6335  
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 Lys Lys Tyr Lys Phe Glu Lys Asp Gly Ser Ile His Arg Leu Ile Ile  
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 6385 6390 6395 6400  
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 Val Phe Leu Ala Glu Leu Asn Lys Asp Lys Val Glu Val Gln Trp Leu  
 6435 6440 6445  
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 Gln Gly Glu Tyr Arg Phe Ile Ala Lys Asp Lys Glu Ala Arg Ala Lys  
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 Thr Lys Thr Ile Asp Thr Thr Ala Glu Gln Thr Ser Phe Arg Ile Leu  
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 6565 6570 6575  
 Lys His Gly Lys Ala Glu Gly Phe Ile Asn Leu Lys Val Ile Asp Val  
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 Pro Gly Pro Val Arg Asn Leu Glu Val Thr Glu Thr Phe Asp Gly Glu  
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 Val Ser Leu Ala Trp Glu Glu Pro Leu Thr Asp Gly Gly Ser Lys Ile  
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 Ile Gly Tyr Val Val Glu Arg Arg Asp Ile Lys Arg Lys Thr Trp Val  
 6625 6630 6635 6640  
 Leu Ala Thr Asp Arg Ala Glu Ser Cys Glu Phe Thr Val Thr Gly Leu  
 6645 6650 6655  
 Gln Lys Gly Gly Val Glu Tyr Leu Phe Arg Val Ser Ala Arg Asn Arg  
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Val Gly Thr Gly Glu Pro Val Glu Thr Asp Asn Pro Val Glu Ala Arg  
 6675 6680 6685  
 Ser Lys Tyr Asp Val Pro Gly Pro Pro Leu Asn Val Thr Ile Thr Asp  
 6690 6695 6700  
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 Pro Pro Leu Lys Asp Gly Gly Ser Pro Ile Leu Gly Tyr Ile Ile Glu  
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 Arg Cys Glu Glu Lys Asp Asn Trp Ile Arg Cys Asn Met Lys Leu  
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 Val Pro Glu Leu Thr Tyr Lys Val Thr Gly Leu Glu Lys Gly Asn Lys  
 6850 6855 6860  
 Tyr Leu Tyr Arg Val Ser Ala Glu Asn Lys Ala Gly Val Ser Asp Pro  
 6865 6870 6875 6880  
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 Thr Met Asp Leu Ser Ala Phe Lys Asp Gly Leu Glu Val Ile Val Pro  
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 Ala Thr Trp Cys Phe Gly Asp Lys Val Leu Glu Thr Gly Asp Arg Val  
 6930 6935 6940  
 Lys Met Lys Thr Leu Ser Ala Tyr Ala Glu Leu Val Ile Ser Pro Ser  
 6945 6950 6955 6960  
 Glu Arg Ser Asp Lys Gly Ile Tyr Thr Leu Lys Leu Glu Asn Arg Val  
 6965 6970 6975  
 Lys Thr Ile Ser Gly Glu Ile Asp Val Asn Val Ile Ala Arg Pro Ser  
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 Ala Pro Lys Glu Leu Lys Phe Gly Asp Ile Thr Lys Asp Ser Val His  
 6995 7000 7005  
 Leu Thr Trp Glu Pro Pro Asp Asp Asp Gly Gly Ser Pro Leu Thr Gly  
 7010 7015 7020  
 Tyr Val Val Glu Lys Arg Glu Val Ser Arg Lys Thr Trp Thr Lys Val  
 7025 7030 7035 7040  
 Met Asp Phe Val Thr Asp Leu Glu Phe Thr Val Pro Asp Leu Val Gln  
 7045 7050 7055  
 Gly Lys Glu Tyr Leu Phe Lys Val Cys Ala Arg Asn Lys Cys Gly Pro  
 7060 7065 7070  
 Gly Glu Pro Ala Tyr Val Asp Glu Pro Val Asn Met Ser Thr Pro Ala  
 7075 7080 7085  
 Thr Val Pro Asp Pro Pro Glu Asn Val Lys Trp Arg Asp Arg Thr Ala  
 7090 7095 7100  
 Asn Ser Ile Phe Leu Thr Trp Asp Pro Pro Lys Asn Asp Gly Gly Ser  
 7105 7110 7115 7120  
 Arg Ile Lys Gly Tyr Ile Val Glu Arg Cys Pro Arg Gly Ser Asp Lys  
 7125 7130 7135  
 Trp Val Ala Cys Gly Glu Pro Val Ala Glu Thr Lys Met Glu Val Thr  
 7140 7145 7150  
 Gly Leu Glu Glu Gly Lys Trp Tyr Ala Tyr Arg Val Lys Thr Leu Asn  
 7155 7160 7165

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Arg Gln Gly Ala Ser Lys Pro Ser Arg Pro Thr Glu Glu Ile Gln Ala
7170          7175          7180
Val Asp Thr Gln Glu Ala Pro Glu Ile Phe Leu Asp Val Lys Leu Leu
7185          7190          7195          7200
Ala Gly Leu Thr Val Lys Ala Gly Thr Lys Ile Glu Leu Pro Ala Thr
          7205          7210          7215
Val Thr Gly Lys Pro Glu Pro Lys Ile Thr Trp Thr Lys Ala Asp Met
          7220          7225          7230
Ile Leu Lys Gln Asp Lys Arg Ile Thr Ile Glu Asn Val Pro Lys Lys
          7235          7240          7245
Ser Thr Val Thr Ile Val Asp Ser Lys Arg Ser Asp Thr Gly Thr Tyr
          7250          7255          7260
Ile Ile Glu Ala Val Asn Val Cys Gly Arg Ala Thr Ala Val Val Glu
7265          7270          7275          7280
Val Asn Val Leu Asp Lys Pro Gly Pro Pro Ala Ala Phe Asp Ile Thr
          7285          7290          7295
Asp Val Thr Asn Glu Ser Cys Leu Leu Thr Trp Asn Pro Pro Arg Asp
          7300          7305          7310
Asp Gly Gly Ser Lys Ile Thr Asn Tyr Val Val Glu Arg Arg Ala Thr
          7315          7320          7325
Asp Ser Glu Val Trp His Lys Leu Ser Ser Thr Val Lys Asp Thr Asn
          7330          7335          7340
Phe Lys Ala Thr Lys Leu Ile Pro Asn Lys Glu Tyr Ile Phe Arg Val
7345          7350          7355          7360
Ala Ala Glu Asn Met Tyr Gly Ala Gly Glu Pro Val Gln Ala Ser Pro
          7365          7370          7375
Ile Thr Ala Lys Tyr Gln Phe Asp Pro Pro Gly Pro Pro Thr Arg Leu
          7380          7385          7390
Glu Pro Ser Asp Ile Thr Lys Asp Ala Val Thr Leu Thr Trp Cys Glu
          7395          7400          7405
Pro Asp Asp Asp Gly Gly Ser Pro Ile Thr Gly Tyr Trp Val Glu Arg
          7410          7415          7420
Leu Asp Pro Asp Thr Asp Lys Trp Val Arg Cys Asn Lys Met Pro Val
7425          7430          7435          7440
Lys Asp Thr Thr Tyr Arg Val Lys Gly Leu Thr Asn Lys Lys Lys Tyr
          7445          7450          7455
Arg Phe Arg Val Leu Ala Glu Asn Leu Ala Gly Pro Gly Lys Pro Ser
          7460          7465          7470
Lys Ser Thr Glu Pro Ile Leu Ile Lys Asp Pro Ile Asp Pro Pro Trp
          7475          7480          7485
Pro Pro Gly Lys Pro Thr Val Lys Asp Val Gly Lys Thr Ser Val Arg
          7490          7495          7500
Leu Asn Trp Thr Lys Pro Glu His Asp Gly Gly Ala Lys Ile Glu Ser
7505          7510          7515          7520
Tyr Val Ile Glu Met Leu Lys Thr Gly Thr Asp Glu Trp Val Arg Val
          7525          7530          7535
Ala Glu Gly Val Pro Thr Thr Gln His Leu Leu Pro Gly Leu Met Glu
          7540          7545          7550
Gly Gln Glu Tyr Ser Phe Arg Val Arg Ala Val Asn Lys Ala Gly Glu
          7555          7560          7565
Ser Glu Pro Ser Glu Pro Ser Asp Pro Val Leu Cys Arg Glu Lys Leu
          7570          7575          7580
Tyr Pro Pro Ser Pro Pro Arg Trp Leu Glu Val Ile Asn Ile Thr Lys
7585          7590          7595          7600
Asn Thr Ala Asp Leu Lys Trp Thr Val Pro Glu Lys Asp Gly Gly Ser
          7605          7610          7615
Pro Ile Thr Asn Tyr Ile Val Glu Lys Arg Asp Val Arg Arg Lys Gly
          7620          7625          7630
Trp Gln Thr Val Asp Thr Thr Val Lys Asp Thr Lys Cys Thr Val Thr
          7635          7640          7645
Pro Leu Thr Glu Gly Ser Leu Tyr Val Phe Arg Val Ala Ala Glu Asn
          7650          7655          7660

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Ala Ile Gly Gln Ser Asp Tyr Thr Glu Ile Glu Asp Ser Val Leu Ala  
 7665 7670 7675 7680  
 Lys Asp Thr Phe Thr Thr Pro Gly Pro Pro Tyr Ala Leu Ala Val Val  
 7685 7690 7695  
 Asp Val Thr Lys Arg His Val Asp Leu Lys Trp Glu Pro Pro Lys Asn  
 7700 7705 7710  
 Asp Gly Gly Arg Pro Ile Gln Arg Tyr Val Ile Glu Lys Lys Glu Arg  
 7715 7720 7725  
 Leu Gly Thr Arg Trp Val Lys Ala Gly Lys Thr Ala Gly Pro Asp Cys  
 7730 7735 7740  
 Asn Phe Arg Val Thr Asp Val Ile Glu Gly Thr Glu Val Gln Phe Gln  
 7745 7750 7755 7760  
 Val Arg Ala Glu Asn Glu Ala Gly Val Gly His Pro Ser Glu Pro Thr  
 7765 7770 7775  
 Glu Ile Leu Ser Ile Glu Asp Pro Thr Ser Pro Pro Ser Pro Pro Leu  
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 Asp Leu His Val Thr Asp Ala Gly Arg Lys His Ile Ala Ile Ala Trp  
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 Lys Pro Pro Glu Lys Asn Gly Gly Ser Pro Ile Ile Glu Tyr His Val  
 7810 7815 7820  
 Glu Met Cys Pro Val Gly Thr Glu Lys Trp Met Arg Val Asn Ser Arg  
 7825 7830 7835 7840  
 Pro Ile Lys Asp Leu Lys Phe Lys Val Glu Glu Gly Val Val Pro Asp  
 7845 7850 7855  
 Lys Glu Tyr Val Leu Arg Val Arg Ala Val Asn Ala Ile Gly Val Ser  
 7860 7865 7870  
 Glu Pro Ser Glu Ile Ser Glu Asn Val Val Ala Lys Asp Pro Asp Cys  
 7875 7880 7885  
 Lys Pro Thr Ile Asp Leu Glu Thr His Asp Ile Ile Val Ile Glu Gly  
 7890 7895 7900  
 Glu Lys Leu Ser Ile Pro Val Pro Phe Arg Ala Val Pro Val Pro Thr  
 7905 7910 7915 7920  
 Val Ser Trp His Lys Asp Gly Lys Glu Val Lys Ala Ser Asp Arg Leu  
 7925 7930 7935  
 Thr Met Lys Asn Asp His Ile Ser Ala His Leu Glu Val Pro Lys Ser  
 7940 7945 7950  
 Val Arg Ala Asp Ala Gly Ile Tyr Thr Ile Thr Leu Glu Asn Lys Leu  
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 Gly Ser Ala Thr Ala Ser Ile Asn Val Lys Val Ile Gly Leu Pro Gly  
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 Pro Cys Lys Asp Ile Lys Ala Ser Asp Ile Thr Lys Ser Ser Cys Lys  
 7985 7990 7995 8000  
 Leu Thr Trp Glu Pro Pro Glu Phe Asp Gly Gly Thr Pro Ile Leu His  
 8005 8010 8015  
 Tyr Val Leu Glu Arg Arg Glu Ala Gly Arg Arg Thr Tyr Ile Pro Val  
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 Met Ser Gly Glu Asn Lys Leu Ser Trp Thr Val Lys Asp Leu Ile Pro  
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 Asn Gly Glu Tyr Phe Phe Arg Val Lys Ala Val Asn Lys Val Gly Gly  
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 Gly Glu Tyr Ile Glu Leu Lys Asn Pro Val Ile Ala Gln Asp Pro Lys  
 8065 8070 8075 8080  
 Gln Pro Pro Asp Pro Pro Val Asp Val Glu Val His Asn Pro Thr Ala  
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 Glu Ala Met Thr Ile Thr Trp Lys Pro Pro Leu Tyr Asp Gly Gly Ser  
 8100 8105 8110  
 Lys Ile Met Gly Tyr Ile Ile Glu Lys Ile Ala Lys Gly Glu Glu Arg  
 8115 8120 8125  
 Trp Lys Arg Cys Asn Glu His Leu Val Pro Ile Leu Thr Tyr Thr Ala  
 8130 8135 8140  
 Lys Gly Leu Glu Glu Gly Lys Glu Tyr Gln Phe Arg Val Arg Ala Glu  
 8145 8150 8155 8160

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Asn Ala Ala Gly Ile Ser Glu Pro Ser Arg Ala Thr Pro Pro Thr Lys
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Ala Val Asp Pro Ile Asp Ala Pro Lys Val Ile Leu Arg Thr Ser Leu
      8180                      8185                      8190
Glu Val Lys Arg Gly Asp Glu Ile Ala Leu Asp Ala Ser Ile Ser Gly
      8195                      8200                      8205
Ser Pro Tyr Pro Thr Ile Thr Trp Ile Lys Asp Glu Asn Val Ile Val
      8210                      8215                      8220
Pro Glu Glu Ile Lys Lys Arg Ala Ala Pro Leu Val Arg Arg Arg Lys
      8225                      8230                      8235                      8240
Gly Glu Val Gln Glu Glu Glu Pro Phe Val Leu Pro Leu Thr Gln Arg
      8245                      8250                      8255
Leu Ser Ile Asp Asn Ser Lys Lys Gly Glu Ser Gln Leu Arg Val Arg
      8260                      8265                      8270
Asp Ser Leu Arg Pro Asp His Gly Leu Tyr Met Ile Lys Val Glu Asn
      8275                      8280                      8285
Asp His Gly Ile Ala Lys Ala Pro Cys Thr Val Ser Val Leu Asp Thr
      8290                      8295                      8300
Pro Gly Pro Pro Ile Asn Phe Val Phe Glu Asp Ile Arg Lys Thr Ser
      8305                      8310                      8315                      8320
Val Leu Cys Lys Trp Glu Pro Pro Leu Asp Asp Gly Gly Ser Glu Ile
      8325                      8330                      8335
Ile Asn Tyr Thr Leu Glu Lys Lys Asp Lys Thr Lys Pro Asp Ser Glu
      8340                      8345                      8350
Trp Ile Val Val Thr Ser Thr Leu Arg His Cys Lys Tyr Ser Val Thr
      8355                      8360                      8365
Lys Leu Ile Glu Gly Lys Glu Tyr Leu Phe Arg Val Arg Ala Glu Asn
      8370                      8375                      8380
Arg Phe Gly Pro Gly Pro Pro Cys Val Ser Lys Pro Leu Val Ala Lys
      8385                      8390                      8395                      8400
Asp Pro Phe Gly Pro Pro Asp Ala Pro Asp Lys Pro Ile Val Glu Asp
      8405                      8410                      8415
Val Thr Ser Asn Ser Met Leu Val Lys Trp Asn Glu Pro Lys Asp Asn
      8420                      8425                      8430
Gly Ser Pro Ile Leu Gly Tyr Trp Leu Glu Lys Arg Glu Val Asn Ser
      8435                      8440                      8445
Thr His Trp Ser Arg Val Asn Lys Ser Leu Leu Asn Ala Leu Lys Ala
      8450                      8455                      8460
Asn Val Asp Gly Leu Leu Glu Gly Leu Thr Tyr Val Phe Arg Val Cys
      8465                      8470                      8475                      8480
Ala Glu Asn Ala Ala Gly Pro Gly Lys Phe Ser Pro Pro Ser Asp Pro
      8485                      8490                      8495
Lys Thr Ala His Asp Pro Ile Ser Pro Pro Gly Pro Pro Ile Pro Arg
      8500                      8505                      8510
Val Thr Asp Thr Ser Ser Thr Thr Ile Glu Leu Glu Trp Glu Pro Pro
      8515                      8520                      8525
Ala Phe Asn Gly Gly Gly Glu Ile Val Gly Tyr Phe Val Asp Lys Gln
      8530                      8535                      8540
Leu Val Gly Thr Asn Lys Trp Ser Arg Cys Thr Glu Lys Met Ile Lys
      8545                      8550                      8555                      8560
Val Arg Gln Tyr Thr Val Lys Glu Ile Arg Glu Gly Ala Asp Tyr Lys
      8565                      8570                      8575
Leu Arg Val Ser Ala Val Asn Ala Ala Gly Glu Gly Pro Pro Gly Glu
      8580                      8585                      8590
Thr Gln Pro Val Thr Val Ala Glu Pro Gln Glu Pro Pro Ala Val Glu
      8595                      8600                      8605
Leu Asp Val Ser Val Lys Gly Gly Ile Gln Ile Met Ala Gly Lys Thr
      8610                      8615                      8620
Leu Arg Ile Pro Ala Val Val Thr Gly Arg Pro Val Pro Thr Lys Val
      8625                      8630                      8635                      8640
Trp Thr Lys Glu Glu Gly Glu Leu Asp Lys Asp Arg Val Val Ile Asp
      8645                      8650                      8655

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Asn Val Gly Thr Lys Ser Glu Leu Ile Ile Lys Asp Ala Leu Arg Lys  
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 Asp His Gly Arg Tyr Val Ile Thr Ala Thr Asn Ser Cys Gly Ser Lys  
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 Phe Ala Ala Ala Arg Val Glu Val Phe Asp Val Pro Gly Pro Val Leu  
 8690 8695 8700  
 Asp Leu Lys Pro Val Val Thr Asn Arg Lys Met Cys Leu Leu Asn Trp  
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 Ser Asp Pro Glu Asp Asp Gly Gly Ser Glu Ile Thr Gly Phe Ile Ile  
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 Glu Arg Lys Asp Ala Lys Met His Thr Trp Arg Gln Pro Ile Glu Thr  
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 Glu Arg Ser Lys Cys Asp Ile Thr Gly Leu Leu Glu Gly Gln Glu Tyr  
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 Ile Ile Glu Lys Arg Arg His Asp Lys Pro Asp Phe Glu Arg Val Asn  
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 Lys Arg Leu Cys Pro Thr Thr Ser Phe Leu Val Glu Asn Leu Asp Glu  
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 His Gln Met Tyr Glu Phe Arg Val Lys Ala Val Asn Glu Ile Gly Glu  
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 Val Lys Ala Gly Glu Pro Val His Ile Pro Ala Asp Val Thr Gly Leu  
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 Pro Met Pro Lys Ile Glu Trp Ser Lys Asn Glu Thr Val Ile Glu Lys  
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 Pro Thr Asp Ala Leu Gln Ile Thr Lys Glu Glu Val Ser Arg Ser Glu  
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 Leu Asp Asn Gly Gly Ser Glu Ile Thr His Tyr Val Ile Asp Lys Arg  
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 Val Glu Lys Arg Tyr Gly Ile Trp Lys Leu Ile Pro Asn Gly Gln Tyr  
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 Lys Ser Asp Lys Val Val Ile Gln Asp Pro Tyr Arg Leu Pro Gly Pro  
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 Ser Trp Thr Pro Pro Leu Asp Asn Gly Gly Ser Pro Ile Thr Gly Tyr  
 9125 9130 9135  
 Trp Leu Glu Lys Arg Glu Glu Gly Ser Pro Tyr Trp Ser Arg Val Ser  
 9140 9145 9150

Arg Ala Pro Ile Thr Lys Val Gly Leu Lys Gly Val Glu Phe Asn Val  
 9155 9160 9165  
 Pro Arg Leu Leu Glu Gly Val Lys Tyr Gln Phe Arg Ala Met Ala Ile  
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 9185 9190 9195 9200  
 Ala Gly Asp Pro Ile Phe Pro Pro Gly Pro Pro Ser Cys Pro Glu Val  
 9205 9210 9215  
 Lys Asp Lys Thr Lys Ser Ser Ile Ser Leu Gly Trp Lys Pro Pro Ala  
 9220 9225 9230  
 Lys Asp Gly Gly Ser Pro Ile Lys Gly Tyr Ile Val Glu Met Gln Glu  
 9235 9240 9245  
 Glu Gly Thr Thr Asp Trp Lys Arg Val Asn Glu Pro Asp Lys Leu Ile  
 9250 9255 9260  
 Thr Thr Cys Glu Cys Val Val Pro Asn Leu Lys Glu Leu Arg Lys Tyr  
 9265 9270 9275 9280  
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 9300 9305 9310  
 Val Phe Ile Asp Ile Gly Ala Gln Asp Cys Leu Val Cys Lys Ala Gly  
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 Ser Gln Ile Arg Ile Pro Ala Val Ile Lys Gly Arg Pro Thr Pro Lys  
 9330 9335 9340  
 Ser Ser Trp Glu Phe Asp Gly Lys Ala Lys Lys Ala Met Lys Asp Gly  
 9345 9350 9355 9360  
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 9365 9370 9375  
 Ser Val Ile Ile Ile Pro Glu Cys Lys Arg Ser His Thr Gly Lys Tyr  
 9380 9385 9390  
 Ser Ile Thr Ala Lys Asn Lys Ala Gly Gln Lys Thr Ala Asn Cys Arg  
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 Val Lys Val Met Asp Val Pro Gly Pro Pro Lys Asp Leu Lys Val Ser  
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 Asp Ile Thr Arg Gly Ser Cys Arg Leu Ser Trp Lys Met Pro Asp Asp  
 9425 9430 9435 9440  
 Asp Gly Gly Asp Arg Ile Lys Gly Tyr Val Ile Glu Lys Arg Thr Ile  
 9445 9450 9455  
 Asp Gly Lys Ala Trp Thr Lys Val Asn Pro Asp Cys Gly Ser Thr Thr  
 9460 9465 9470  
 Phe Val Val Pro Asp Leu Leu Ser Glu Gln Gln Tyr Phe Phe Arg Val  
 9475 9480 9485  
 Arg Ala Glu Asn Arg Phe Gly Ile Gly Pro Pro Val Glu Thr Ile Gln  
 9490 9495 9500  
 Arg Thr Thr Ala Arg Asp Pro Ile Tyr Pro Pro Asp Pro Pro Ile Lys  
 9505 9510 9515 9520  
 Leu Lys Ile Gly Leu Ile Thr Lys Asn Thr Val His Leu Ser Trp Lys  
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 Pro Pro Lys Asn Asp Gly Gly Ser Pro Val Thr His Tyr Ile Val Glu  
 9540 9545 9550  
 Cys Leu Ala Trp Asp Pro Thr Gly Thr Lys Lys Glu Ala Trp Arg Gln  
 9555 9560 9565  
 Cys Asn Lys Arg Asp Val Glu Glu Leu Gln Phe Thr Val Glu Asp Leu  
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 Val Glu Gly Gly Glu Tyr Glu Phe Arg Val Lys Ala Val Asn Ala Ala  
 9585 9590 9595 9600  
 Gly Val Ser Lys Pro Ser Ala Thr Val Gly Pro Cys Asp Cys Gln Arg  
 9605 9610 9615  
 Pro Asp Met Pro Pro Ser Ile Asp Leu Lys Glu Phe Met Glu Val Glu  
 9620 9625 9630  
 Glu Gly Thr Asn Val Asn Ile Val Ala Lys Ile Lys Gly Val Pro Phe  
 9635 9640 9645

Pro Thr Leu Thr Trp Phe Lys Ala Pro Pro Lys Lys Pro Asp Asn Lys  
 9650 9655 9660  
 Glu Pro Val Leu Tyr Asp Thr His Val Asn Lys Leu Val Val Asp Asp  
 9665 9670 9675 9680  
 Thr Cys Thr Leu Val Ile Pro Gln Ser Arg Arg Ser Asp Thr Gly Leu  
 9685 9690 9695  
 Tyr Thr Ile Thr Ala Val Asn Asn Leu Gly Thr Ala Ser Lys Glu Met  
 9700 9705 9710  
 Arg Leu Asn Val Leu Gly Arg Pro Gly Pro Pro Val Gly Pro Ile Lys  
 9715 9720 9725  
 Phe Glu Ser Val Ser Ala Asp Gln Met Thr Leu Ser Trp Phe Pro Pro  
 9730 9735 9740  
 Lys Asp Asp Gly Gly Ser Lys Ile Thr Asn Tyr Val Ile Glu Lys Arg  
 9745 9750 9755 9760  
 Glu Ala Asn Arg Lys Thr Trp Val His Val Ser Ser Glu Pro Lys Glu  
 9765 9770 9775  
 Cys Thr Tyr Thr Ile Pro Lys Leu Leu Glu Gly His Glu Tyr Val Phe  
 9780 9785 9790  
 Arg Ile Met Ala Gln Asn Lys Tyr Gly Ile Gly Glu Pro Leu Asp Ser  
 9795 9800 9805  
 Glu Pro Glu Thr Ala Arg Asn Leu Phe Ser Val Pro Gly Ala Pro Asp  
 9810 9815 9820  
 Lys Pro Thr Val Ser Ser Val Thr Arg Asn Ser Met Thr Val Asn Trp  
 9825 9830 9835 9840  
 Glu Glu Pro Glu Tyr Asp Gly Gly Ser Pro Val Thr Gly Tyr Trp Leu  
 9845 9850 9855  
 Glu Met Lys Asp Thr Thr Ser Lys Arg Trp Lys Arg Val Asn Arg Asp  
 9860 9865 9870  
 Pro Ile Lys Ala Met Thr Leu Gly Val Ser Tyr Lys Val Thr Gly Leu  
 9875 9880 9885  
 Ile Glu Gly Ser Asp Tyr Gln Phe Arg Val Tyr Ala Ile Asn Ala Ala  
 9890 9895 9900  
 Gly Val Gly Pro Ala Ser Leu Pro Ser Asp Pro Ala Thr Ala Arg Asp  
 9905 9910 9915 9920  
 Pro Ile Ala Pro Pro Gly Pro Pro Phe Pro Lys Val Thr Asp Trp Thr  
 9925 9930 9935  
 Lys Ser Ser Ala Asp Leu Glu Trp Ser Pro Pro Leu Lys Asp Gly Gly  
 9940 9945 9950  
 Ser Lys Val Thr Gly Tyr Ile Val Glu Tyr Lys Glu Glu Gly Lys Glu  
 9955 9960 9965  
 Glu Trp Glu Lys Gly Lys Asp Lys Glu Val Arg Gly Thr Lys Leu Val  
 9970 9975 9980  
 Val Thr Gly Leu Lys Glu Gly Ala Phe Tyr Lys Phe Arg Val Ser Ala  
 9985 9990 9995 10000  
 Val Asn Ile Ala Gly Ile Gly Glu Pro Gly Glu Val Thr Asp Val Ile  
 10005 10010 10015  
 Glu Met Lys Asp Arg Leu Val Ser Pro Asp Leu Gln Leu Asp Ala Ser  
 10020 10025 10030  
 Val Arg Asp Arg Ile Val Val His Ala Gly Gly Val Ile Arg Ile Ile  
 10035 10040 10045  
 Ala Tyr Val Ser Gly Lys Pro Pro Pro Thr Val Thr Trp Asn Met Asn  
 10050 10055 10060 1  
 Glu Arg Thr Leu Pro Gln Glu Ala Thr Ile Glu Thr Thr Ala Ile Ser  
 0065 10070 10075 10080  
 Ser Ser Met Val Ile Lys Asn Cys Gln Arg Ser His Gln Gly Val Tyr  
 10085 10090 10095  
 Ser Leu Leu Ala Lys Asn Glu Ala Gly Glu Arg Lys Lys Thr Ile Ile  
 10100 10105 10110  
 Val Asp Val Leu Asp Val Pro Gly Pro Val Gly Thr Pro Phe Leu Ala  
 10115 10120 10125  
 His Asn Leu Thr Asn Glu Ser Cys Lys Leu Thr Trp Phe Ser Pro Glu  
 10130 10135 10140 1

Asp Asp Gly Gly Ser Pro Ile Thr Asn Tyr Val Ile Glu Lys Arg Glu  
 0145 10150 10155 10160  
 Ser Asp Arg Arg Ala Trp Thr Pro Val Thr Tyr Thr Val Thr Arg Gln  
 10165 10170 10175  
 Asn Ala Thr Val Gln Gly Leu Ile Gln Gly Lys Ala Tyr Phe Phe Arg  
 10180 10185 10190  
 Ile Ala Ala Glu Asn Ser Ile Gly Met Gly Pro Phe Val Glu Thr Ser  
 10195 10200 10205  
 Glu Ala Leu Val Ile Arg Glu Pro Ile Thr Val Pro Glu Arg Pro Glu  
 10210 10215 10220 1  
 Asp Leu Glu Val Lys Glu Val Thr Lys Asn Thr Val Thr Leu Thr Trp  
 0225 10230 10235 10240  
 Asn Pro Pro Lys Tyr Asp Gly Gly Ser Glu Ile Ile Asn Tyr Val Leu  
 10245 10250 10255  
 Glu Ser Arg Leu Ile Gly Thr Glu Lys Phe His Lys Val Thr Asn Asp  
 10260 10265 10270  
 Asn Leu Leu Ser Arg Lys Tyr Thr Val Lys Gly Leu Lys Glu Gly Asp  
 10275 10280 10285  
 Thr Tyr Glu Tyr Arg Val Ser Ala Val Asn Ile Val Gly Gln Gly Lys  
 10290 10295 10300 1  
 Pro Ser Phe Cys Thr Lys Pro Ile Thr Cys Lys Asp Glu Leu Ala Pro  
 0305 10310 10315 10320  
 Pro Thr Leu His Leu Asp Phe Arg Asp Lys Leu Thr Ile Arg Val Gly  
 10325 10330 10335  
 Glu Ala Phe Ala Leu Thr Gly Arg Tyr Ser Gly Lys Pro Lys Pro Lys  
 10340 10345 10350  
 Val Ser Trp Phe Lys Asp Glu Ala Asp Val Leu Glu Asp Asp Arg Thr  
 10355 10360 10365  
 His Ile Lys Thr Thr Pro Ala Thr Leu Ala Leu Glu Lys Ile Lys Ala  
 10370 10375 10380 1  
 Lys Arg Ser Asp Ser Gly Lys Tyr Cys Val Val Val Glu Asn Ser Thr  
 0385 10390 10395 10400  
 Gly Ser Arg Lys Gly Phe Cys Gln Val Asn Val Val Asp His Pro Gly  
 10405 10410 10415  
 Pro Pro Val Gly Pro Val Ser Phe Asp Glu Val Thr Lys Asp Tyr Met  
 10420 10425 10430  
 Val Ile Ser Trp Lys Pro Pro Leu Asp Asp Gly Gly Ser Lys Ile Thr  
 10435 10440 10445  
 Asn Tyr Ile Ile Glu Lys Lys Glu Val Gly Lys Asp Val Trp Met Pro  
 10450 10455 10460 1  
 Val Thr Ser Ala Ser Ala Lys Thr Thr Cys Lys Val Ser Lys Leu Leu  
 0465 10470 10475 10480  
 Glu Gly Lys Asp Tyr Ile Phe Arg Ile His Ala Glu Asn Leu Tyr Gly  
 10485 10490 10495  
 Ile Ser Asp Pro Leu Val Ser Asp Ser Met Lys Ala Lys Asp Arg Phe  
 10500 10505 10510  
 Arg Val Pro Asp Ala Pro Asp Gln Pro Ile Val Thr Glu Val Thr Lys  
 10515 10520 10525  
 Asp Ser Ala Leu Val Thr Trp Asn Lys Pro His Asp Gly Gly Lys Pro  
 10530 10535 10540 1  
 Ile Thr Asn Tyr Ile Leu Glu Lys Arg Glu Thr Met Ser Lys Arg Trp  
 0545 10550 10555 10560  
 Ala Arg Val Thr Lys Asp Pro Ile His Pro Tyr Thr Lys Phe Arg Val  
 10565 10570 10575  
 Pro Asp Leu Leu Glu Gly Cys Gln Tyr Glu Phe Arg Val Ser Ala Glu  
 10580 10585 10590  
 Asn Glu Ile Gly Ile Gly Asp Pro Ser Pro Pro Ser Lys Pro Val Phe  
 10595 10600 10605  
 Ala Lys Asp Pro Ile Ala Lys Pro Ser Pro Pro Val Asn Pro Glu Ala  
 10610 10615 10620 1  
 Ile Asp Thr Thr Cys Asn Ser Val Asp Leu Thr Trp Gln Pro Pro Arg  
 0625 10630 10635 10640

His Asp Gly Gly Ser Lys Ile Leu Gly Tyr Ile Val Glu Tyr Gln Lys  
 10645 10650 10655  
 Val Gly Asp Glu Glu Trp Arg Arg Ala Asn His Thr Pro Glu Ser Cys  
 10660 10665 10670  
 Pro Glu Thr Lys Tyr Lys Val Thr Gly Leu Arg Asp Gly Gln Thr Tyr  
 10675 10680 10685  
 Lys Phe Arg Val Leu Ala Val Asn Ala Ala Gly Glu Ser Asp Pro Ala  
 10690 10695 10700 1  
 His Val Pro Glu Pro Val Leu Val Lys Asp Arg Leu Glu Pro Pro Glu  
 0705 10710 10715 10720  
 Leu Ile Leu Asp Ala Asn Met Ala Arg Glu Gln His Ile Lys Val Gly  
 10725 10730 10735  
 Asp Thr Leu Arg Leu Ser Ala Ile Ile Lys Gly Val Pro Phe Pro Lys  
 10740 10745 10750  
 Val Thr Trp Lys Lys Glu Asp Arg Asp Ala Pro Thr Lys Ala Arg Ile  
 10755 10760 10765  
 Asp Val Thr Pro Val Gly Ser Lys Leu Glu Ile Arg Asn Ala Ala His  
 10770 10775 10780 1  
 Glu Asp Gly Gly Ile Tyr Ser Leu Thr Val Glu Asn Pro Ala Gly Ser  
 0785 10790 10795 10800  
 Lys Thr Val Ser Val Lys Val Leu Val Leu Asp Lys Pro Gly Pro Pro  
 10805 10810 10815  
 Arg Asp Leu Glu Val Ser Glu Ile Arg Lys Asp Ser Cys Tyr Leu Thr  
 10820 10825 10830  
 Trp Lys Glu Pro Leu Asp Asp Gly Gly Ser Val Ile Thr Asn Tyr Val  
 10835 10840 10845  
 Val Glu Arg Arg Asp Val Ala Ser Ala Gln Trp Ser Pro Leu Ser Ala  
 10850 10855 10860 1  
 Thr Ser Lys Lys Lys Ser His Phe Ala Lys His Leu Asn Glu Gly Asn  
 0865 10870 10875 10880  
 Gln Tyr Leu Phe Arg Val Ala Ala Glu Asn Gln Tyr Gly Arg Gly Pro  
 10885 10890 10895  
 Phe Val Glu Thr Pro Lys Pro Ile Lys Ala Leu Asp Pro Leu His Pro  
 10900 10905 10910  
 Pro Gly Pro Pro Lys Asp Leu His His Val Asp Val Asp Lys Thr Glu  
 10915 10920 10925  
 Val Ser Leu Val Trp Asn Lys Pro Asp Arg Asp Gly Gly Ser Pro Ile  
 10930 10935 10940 1  
 Thr Gly Tyr Leu Val Glu Tyr Gln Glu Glu Gly Thr Gln Asp Trp Ile  
 0945 10950 10955 10960  
 Lys Phe Lys Thr Val Thr Asn Leu Glu Cys Val Val Thr Gly Leu Gln  
 10965 10970 10975  
 Gln Gly Lys Thr Tyr Arg Phe Arg Val Lys Ala Glu Asn Ile Val Gly  
 10980 10985 10990  
 Leu Gly Leu Pro Asp Thr Thr Ile Pro Ile Glu Cys Gln Glu Lys Leu  
 10995 11000 11005  
 Val Pro Pro Ser Val Glu Leu Asp Val Lys Leu Ile Glu Gly Leu Val  
 11010 11015 11020 1  
 Val Lys Ala Gly Thr Thr Val Arg Phe Pro Ala Ile Ile Arg Gly Val  
 1025 11030 11035 11040  
 Pro Val Pro Thr Ala Lys Trp Thr Thr Asp Gly Ser Glu Ile Lys Thr  
 11045 11050 11055  
 Asp Glu His Tyr Thr Val Glu Thr Asp Asn Phe Ser Ser Val Leu Thr  
 11060 11065 11070  
 Ile Lys Asn Cys Leu Arg Arg Asp Thr Gly Glu Tyr Gln Ile Thr Val  
 11075 11080 11085  
 Ser Asn Ala Ala Gly Ser Lys Thr Val Ala Val His Leu Thr Val Leu  
 11090 11095 11100 1  
 Asp Val Pro Gly Pro Pro Thr Gly Pro Ile Asn Ile Leu Asp Val Thr  
 1105 11110 11115 11120  
 Pro Glu His Met Thr Ile Ser Trp Gln Pro Pro Lys Asp Asp Gly Gly  
 11125 11130 11135

Ser Pro Val Ile Asn Tyr Ile Val Glu Lys Gln Asp Thr Arg Lys Asp  
 11140 11145 11150  
 Thr Trp Gly Val Val Ser Ser Gly Ser Ser Lys Thr Lys Leu Lys Ile  
 11155 11160 11165  
 Pro His Leu Gln Lys Gly Cys Glu Tyr Val Phe Arg Val Arg Ala Glu  
 11170 11175 11180 1  
 Asn Lys Ile Gly Val Gly Pro Pro Leu Asp Ser Thr Pro Thr Val Ala  
 1185 11190 11195 11200  
 Lys His Lys Phe Ser Pro Pro Ser Pro Pro Gly Lys Pro Val Val Thr  
 11205 11210 11215  
 Asp Ile Thr Glu Asn Ala Ala Thr Val Ser Trp Thr Leu Pro Lys Ser  
 11220 11225 11230  
 Asp Gly Gly Ser Pro Ile Thr Gly Tyr Tyr Met Glu Arg Arg Glu Val  
 11235 11240 11245  
 Thr Gly Lys Trp Val Arg Val Asn Lys Thr Pro Ile Ala Asp Leu Lys  
 11250 11255 11260 1  
 Phe Arg Val Thr Gly Leu Tyr Glu Gly Asn Thr Tyr Glu Phe Arg Val  
 1265 11270 11275 11280  
 Phe Ala Glu Asn Leu Ala Gly Leu Ser Lys Pro Ser Pro Ser Ser Asp  
 11285 11290 11295  
 Pro Ile Lys Ala Cys Arg Pro Ile Lys Pro Pro Gly Pro Pro Ile Asn  
 11300 11305 11310  
 Pro Lys Leu Lys Asp Lys Ser Arg Glu Thr Ala Asp Leu Val Trp Thr  
 11315 11320 11325  
 Lys Pro Leu Ser Asp Gly Gly Ser Pro Ile Leu Gly Tyr Val Val Glu  
 11330 11335 11340 1  
 Cys Gln Lys Pro Gly Thr Ala Gln Trp Asn Arg Ile Asn Lys Asp Glu  
 1345 11350 11355 11360  
 Leu Ile Arg Gln Cys Ala Phe Arg Val Pro Gly Leu Ile Glu Gly Asn  
 11365 11370 11375  
 Glu Tyr Arg Phe Arg Ile Lys Ala Ala Asn Ile Val Gly Glu Gly Glu  
 11380 11385 11390  
 Pro Arg Glu Leu Ala Glu Ser Val Ile Ala Lys Asp Ile Leu His Pro  
 11395 11400 11405  
 Pro Glu Val Glu Leu Asp Val Thr Cys Arg Asp Val Ile Thr Val Arg  
 11410 11415 11420 1  
 Val Gly Gln Thr Ile Arg Ile Leu Ala Arg Val Lys Gly Arg Pro Glu  
 1425 11430 11435 11440  
 Pro Asp Ile Thr Trp Thr Lys Glu Gly Lys Val Leu Val Arg Glu Lys  
 11445 11450 11455  
 Arg Val Asp Leu Ile Gln Asp Leu Pro Arg Val Glu Leu Gln Ile Lys  
 11460 11465 11470  
 Glu Ala Val Arg Ala Asp His Gly Lys Tyr Ile Ile Ser Ala Lys Asn  
 11475 11480 11485  
 Ser Ser Gly His Ala Gln Gly Ser Ala Ile Val Asn Val Leu Asp Arg  
 11490 11495 11500 1  
 Pro Gly Pro Cys Gln Asn Leu Lys Val Thr Asn Val Thr Lys Glu Asn  
 1505 11510 11515 11520  
 Cys Thr Ile Ser Trp Glu Asn Pro Leu Asp Asn Gly Gly Ser Glu Ile  
 11525 11530 11535  
 Thr Asn Phe Ile Val Glu Tyr Arg Lys Pro Asn Gln Lys Gly Trp Ser  
 11540 11545 11550  
 Ile Val Ala Ser Asp Val Thr Lys Arg Leu Ile Lys Ala Asn Leu Leu  
 11555 11560 11565  
 Ala Asn Asn Glu Tyr Tyr Phe Arg Val Cys Ala Glu Asn Lys Val Gly  
 11570 11575 11580 1  
 Val Gly Pro Thr Ile Glu Thr Lys Thr Pro Ile Leu Ala Ile Asn Pro  
 1585 11590 11595 11600  
 Ile Asp Arg Pro Gly Glu Pro Glu Asn Leu His Ile Ala Asp Lys Gly  
 11605 11610 11615  
 Lys Thr Phe Val Tyr Leu Lys Trp Arg Arg Pro Asp Tyr Asp Gly Gly  
 11620 11625 11630



Ser Pro Asn Leu Ser Tyr His Val Glu Arg Arg Leu Lys Gly Ser Asp  
 11635 11640 11645  
 Asp Trp Glu Arg Val His Lys Gly Ser Ile Lys Glu Thr His Tyr Met  
 11650 11655 11660 1  
 Val Asp Arg Cys Val Glu Asn Gln Ile Tyr Glu Phe Arg Val Gln Thr  
 1665 11670 11675 11680  
 Lys Asn Glu Gly Gly Glu Ser Asp Trp Val Lys Thr Glu Glu Val Val  
 11685 11690 11695  
 Val Lys Glu Asp Leu Gln Lys Pro Val Leu Asp Leu Lys Leu Ser Gly  
 11700 11705 11710  
 Val Leu Thr Val Lys Ala Gly Asp Thr Ile Arg Leu Glu Ala Gly Val  
 11715 11720 11725  
 Arg Gly Lys Pro Phe Pro Glu Val Ala Trp Thr Lys Asp Lys Asp Ala  
 11730 11735 11740 1  
 Thr Asp Leu Thr Arg Ser Pro Arg Val Lys Ile Asp Thr Arg Ala Asp  
 1745 11750 11755 11760  
 Ser Ser Lys Phe Ser Leu Thr Lys Ala Lys Arg Ser Asp Gly Gly Lys  
 11765 11770 11775  
 Tyr Val Val Thr Ala Thr Asn Thr Ala Gly Ser Phe Val Ala Tyr Ala  
 11780 11785 11790  
 Thr Val Asn Val Leu Asp Lys Pro Gly Pro Val Arg Asn Leu Lys Ile  
 11795 11800 11805  
 Val Asp Val Ser Ser Asp Arg Cys Thr Val Cys Trp Asp Pro Pro Glu  
 11810 11815 11820 1  
 Asp Asp Gly Gly Cys Glu Ile Gln Asn Tyr Ile Leu Glu Lys Cys Glu  
 1825 11830 11835 11840  
 Thr Lys Arg Met Val Trp Ser Thr Tyr Ser Ala Thr Val Leu Thr Pro  
 11845 11850 11855  
 Gly Thr Thr Val Thr Arg Leu Ile Glu Gly Asn Glu Tyr Ile Phe Arg  
 11860 11865 11870  
 Val Arg Ala Glu Asn Lys Ile Gly Thr Gly Pro Pro Thr Glu Ser Lys  
 11875 11880 11885  
 Pro Val Ile Ala Lys Thr Lys Tyr Asp Lys Pro Gly Arg Pro Asp Pro  
 11890 11895 11900 1  
 Pro Glu Val Thr Lys Val Ser Lys Glu Glu Met Thr Val Val Trp Asn  
 1905 11910 11915 11920  
 Pro Pro Glu Tyr Asp Gly Gly Lys Ser Ile Thr Gly Tyr Phe Leu Glu  
 11925 11930 11935  
 Lys Lys Glu Lys His Ser Thr Arg Trp Val Pro Val Asn Lys Ser Ala  
 11940 11945 11950  
 Ile Pro Glu Arg Arg Met Lys Val Gln Asn Leu Leu Pro Asp His Glu  
 11955 11960 11965  
 Tyr Gln Phe Arg Val Lys Ala Glu Asn Glu Ile Gly Ile Gly Glu Pro  
 11970 11975 11980 1  
 Ser Leu Pro Ser Arg Pro Val Val Ala Lys Asp Pro Ile Glu Pro Pro  
 1985 11990 11995 12000  
 Gly Pro Pro Thr Asn Phe Arg Val Val Asp Thr Thr Lys His Ser Ile  
 12005 12010 12015  
 Thr Leu Gly Trp Gly Lys Pro Val Tyr Asp Gly Gly Ala Pro Ile Ile  
 12020 12025 12030  
 Gly Tyr Val Val Glu Met Arg Pro Lys Ile Ala Asp Ala Ser Pro Asp  
 12035 12040 12045  
 Glu Gly Trp Lys Arg Cys Asn Ala Ala Ala Gln Leu Val Arg Lys Glu  
 12050 12055 12060 1  
 Phe Thr Val Thr Ser Leu Asp Glu Asn Gln Glu Tyr Glu Phe Arg Val  
 2065 12070 12075 12080  
 Cys Ala Gln Asn Gln Val Gly Ile Gly Arg Pro Ala Glu Leu Lys Glu  
 12085 12090 12095  
 Ala Ile Lys Pro Lys Glu Ile Leu Glu Pro Pro Glu Ile Asp Leu Asp  
 12100 12105 12110  
 Ala Ser Met Arg Lys Leu Val Ile Val Arg Ala Gly Cys Pro Ile Arg  
 12115 12120 12125

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Leu Phe Ala Ile Val Arg Gly Arg Pro Ala Pro Lys Val Thr Trp Arg
12130          12135          12140          1
Lys Val Gly Ile Asp Asn Val Val Arg Lys Gly Gln Val Asp Leu Val
2145          12150          12155          12160
Asp Thr Met Ala Phe Leu Val Ile Pro Asn Ser Thr Arg Asp Asp Ser
          12165          12170          12175
Gly Lys Tyr Ser Leu Thr Leu Val Asn Pro Ala Gly Glu Lys Ala Val
12180          12185          12190
Phe Val Asn Val Arg Val Leu Asp Thr Pro Gly Pro Val Ser Asp Leu
12195          12200          12205
Lys Val Ser Asp Val Thr Lys Thr Ser Cys His Val Ser Trp Ala Pro
12210          12215          12220          1
Pro Glu Asn Asp Gly Gly Ser Gln Val Thr His Tyr Ile Val Glu Lys
2225          12230          12235          12240
Arg Glu Ala Asp Arg Lys Thr Trp Ser Thr Val Thr Pro Glu Val Lys
          12245          12250          12255
Lys Thr Ser Phe His Val Thr Asn Leu Val Pro Gly Asn Glu Tyr Tyr
12260          12265          12270
Phe Arg Val Thr Ala Val Asn Glu Tyr Gly Pro Gly Val Pro Thr Asp
12275          12280          12285
Val Pro Lys Pro Val Leu Ala Ser Asp Pro Leu Ser Glu Pro Asp Pro
12290          12295          12300          1
Pro Arg Lys Leu Glu Ala Thr Glu Met Thr Lys Asn Ser Ala Thr Leu
2305          12310          12315          12320
Ala Trp Leu Pro Pro Leu Arg Asp Gly Gly Ala Lys Ile Asp Gly Tyr
          12325          12330          12335
Ile Ile Ser Tyr Arg Glu Glu Glu Gln Pro Ala Asp Arg Trp Thr Glu
12340          12345          12350
Tyr Ser Val Val Lys Asp Leu Ser Leu Val Val Thr Gly Leu Lys Glu
12355          12360          12365
Gly Lys Lys Tyr Lys Phe Arg Val Ala Ala Arg Asn Ala Val Gly Val
12370          12375          12380          1
Ser Leu Pro Arg Glu Ala Glu Gly Val Tyr Glu Ala Lys Glu Gln Leu
2385          12390          12395          12400
Leu Pro Pro Lys Ile Leu Met Pro Glu Gln Ile Thr Ile Lys Ala Gly
          12405          12410          12415
Lys Lys Leu Arg Ile Glu Ala His Val Tyr Gly Lys Pro His Pro Thr
12420          12425          12430
Cys Lys Trp Lys Lys Gly Glu Asp Glu Val Val Thr Ser Ser His Leu
12435          12440          12445
Ala Val His Lys Ala Asp Ser Ser Ser Ile Leu Ile Ile Lys Asp Val
12450          12455          12460          1
Thr Arg Lys Asp Ser Gly Tyr Tyr Ser Leu Thr Ala Glu Asn Ser Ser
2465          12470          12475          12480
Gly Thr Asp Thr Gln Lys Ile Lys Val Val Val Met Asp Ala Pro Gly
          12485          12490          12495
Pro Pro Gln Pro Pro Phe Asp Ile Ser Asp Ile Asp Ala Asp Ala Cys
12500          12505          12510
Ser Leu Ser Trp His Ile Pro Leu Glu Asp Gly Gly Ser Asn Ile Thr
12515          12520          12525
Asn Tyr Ile Val Glu Lys Cys Asp Val Ser Arg Gly Asp Trp Val Thr
12530          12535          12540          1
Ala Leu Ala Ser Val Thr Lys Thr Ser Cys Arg Val Gly Lys Leu Ile
2545          12550          12555          12560
Pro Gly Gln Glu Tyr Ile Phe Arg Val Arg Ala Glu Asn Arg Phe Gly
          12565          12570          12575
Ile Ser Glu Pro Leu Thr Ser Pro Lys Met Val Ala Gln Phe Pro Phe
12580          12585          12590
Gly Val Pro Ser Glu Pro Lys Asn Ala Arg Val Thr Lys Val Asn Lys
12595          12600          12605
Asp Cys Ile Phe Val Ala Trp Asp Arg Pro Asp Ser Asp Gly Gly Ser
12610          12615          12620          1

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Pro Ile Ile Gly Tyr Leu Ile Glu Arg Lys Glu Arg Asn Ser Leu Leu  
 2625 12630 12635 12640  
 Trp Val Lys Ala Asn Asp Thr Leu Val Arg Ser Thr Glu Tyr Pro Cys  
 12645 12650 12655  
 Ala Gly Leu Val Glu Gly Leu Glu Tyr Ser Phe Arg Ile Tyr Ala Leu  
 12660 12665 12670  
 Asn Lys Ala Gly Ser Ser Pro Pro Ser Lys Pro Thr Glu Tyr Val Thr  
 12675 12680 12685  
 Ala Arg Met Pro Val Asp Pro Pro Gly Lys Pro Glu Val Ile Asp Val  
 12690 12695 12700 1  
 Thr Lys Ser Thr Val Ser Leu Ile Trp Ala Arg Pro Lys His Asp Gly  
 2705 12710 12715 12720  
 Gly Ser Lys Ile Ile Gly Tyr Phe Val Glu Ala Cys Lys Leu Pro Gly  
 12725 12730 12735  
 Asp Lys Trp Val Arg Cys Asn Thr Ala Pro His Gln Ile Pro Gln Glu  
 12740 12745 12750  
 Glu Tyr Thr Ala Thr Gly Leu Glu Glu Lys Ala Gln Tyr Gln Phe Arg  
 12755 12760 12765  
 Ala Ile Ala Arg Thr Ala Val Asn Ile Ser Pro Pro Ser Glu Pro Ser  
 12770 12775 12780 1  
 Asp Pro Val Thr Ile Leu Ala Glu Asn Val Pro Pro Arg Ile Asp Leu  
 2785 12790 12795 12800  
 Ser Val Ala Met Lys Ser Leu Leu Thr Val Lys Ala Gly Thr Asn Val  
 12805 12810 12815  
 Cys Leu Asp Ala Thr Val Phe Gly Lys Pro Met Pro Thr Val Ser Trp  
 12820 12825 12830  
 Lys Lys Asp Gly Thr Leu Leu Lys Pro Ala Glu Gly Ile Lys Met Ala  
 12835 12840 12845  
 Met Gln Arg Asn Leu Cys Thr Leu Glu Leu Phe Ser Val Asn Arg Lys  
 12850 12855 12860 1  
 Asp Ser Gly Asp Tyr Thr Ile Thr Ala Glu Asn Ser Ser Gly Ser Lys  
 2865 12870 12875 12880  
 Ser Ala Thr Ile Lys Leu Lys Val Leu Asp Lys Pro Gly Pro Pro Ala  
 12885 12890 12895  
 Ser Val Lys Ile Asn Lys Met Tyr Ser Asp Arg Ala Met Leu Ser Trp  
 12900 12905 12910  
 Glu Pro Pro Leu Glu Asp Gly Gly Ser Glu Ile Thr Asn Tyr Ile Val  
 12915 12920 12925  
 Asp Lys Arg Glu Thr Ser Arg Pro Asn Trp Ala Gln Val Ser Ala Thr  
 12930 12935 12940 1  
 Val Pro Ile Thr Ser Cys Ser Val Glu Lys Leu Ile Glu Gly His Glu  
 2945 12950 12955 12960  
 Tyr Gln Phe Arg Ile Cys Ala Glu Asn Lys Tyr Gly Val Gly Asp Pro  
 12965 12970 12975  
 Val Phe Thr Glu Pro Ala Ile Ala Lys Asn Pro Tyr Asp Pro Pro Gly  
 12980 12985 12990  
 Arg Cys Asp Pro Pro Val Ile Ser Asn Ile Thr Lys Asp His Met Thr  
 12995 13000 13005  
 Val Ser Trp Lys Pro Pro Ala Asp Asp Gly Gly Ser Pro Ile Thr Gly  
 13010 13015 13020 1  
 Tyr Leu Leu Glu Lys Arg Glu Thr Gln Ala Val Asn Trp Thr Lys Val  
 3025 13030 13035 13040  
 Asn Arg Lys Pro Ile Ile Glu Arg Thr Leu Lys Ala Thr Gly Leu Gln  
 13045 13050 13055  
 Glu Gly Thr Glu Tyr Glu Phe Arg Val Thr Ala Ile Asn Lys Ala Gly  
 13060 13065 13070  
 Pro Gly Lys Pro Ser Asp Ala Ser Lys Ala Ala Tyr Ala Arg Asp Pro  
 13075 13080 13085  
 Gln Tyr Pro Pro Ala Pro Pro Ala Phe Pro Lys Val Tyr Asp Thr Thr  
 13090 13095 13100 1  
 Arg Ser Ser Val Ser Leu Ser Trp Gly Lys Pro Ala Tyr Asp Gly Gly  
 3105 13110 13115 13120

Ser Pro Ile Ile Gly Tyr Leu Val Glu Val Lys Arg Ala Asp Ser Asp  
 13125 13130 13135  
 Asn Trp Val Arg Cys Asn Leu Pro Gln Asn Leu Gln Lys Thr Arg Phe  
 13140 13145 13150  
 Glu Val Thr Gly Leu Met Glu Asp Thr Gln Tyr Gln Phe Arg Val Tyr  
 13155 13160 13165  
 Ala Val Asn Lys Ile Gly Tyr Ser Asp Pro Ser Asp Val Pro Asp Lys  
 13170 13175 13180 1  
 His Tyr Pro Lys Asp Ile Leu Ile Pro Pro Glu Gly Glu His Asp Ala  
 3185 13190 13195 13200  
 Asp Leu Arg Lys Thr Leu Ile Leu Arg Ala Gly Val Thr Met Arg Leu  
 13205 13210 13215  
 Tyr Val Pro Val Lys Gly Arg Pro Pro Lys Ile Thr Trp Ser Lys  
 13220 13225 13230  
 Pro Asn Val Asn Leu Arg Asp Arg Ile Gly Leu Asp Ile Lys Ser Thr  
 13235 13240 13245  
 Asp Phe Asp Thr Phe Leu Arg Cys Glu Asn Val Asn Lys Tyr Asp Ala  
 13250 13255 13260 1  
 Gly Lys Tyr Ile Leu Thr Leu Glu Asn Ser Cys Gly Lys Lys Glu Tyr  
 3265 13270 13275 13280  
 Thr Ile Val Val Lys Val Leu Asp Thr Pro Gly Pro Pro Ile Asn Val  
 13285 13290 13295  
 Thr Val Lys Glu Ile Ser Lys Asp Ser Ala Tyr Val Thr Trp Glu Pro  
 13300 13305 13310  
 Pro Ile Ile Asp Gly Gly Ser Pro Ile Ile Asn Tyr Val Val Gln Lys  
 13315 13320 13325  
 Arg Asp Ala Glu Arg Lys Ser Trp Ser Thr Val Thr Thr Glu Cys Ser  
 13330 13335 13340 1  
 Lys Thr Ser Phe Arg Val Pro Asn Leu Glu Glu Gly Lys Ser Tyr Phe  
 3345 13350 13355 13360  
 Phe Arg Val Phe Ala Glu Asn Glu Tyr Gly Ile Gly Asp Pro Gly Glu  
 13365 13370 13375  
 Thr Arg Asp Ala Val Lys Ala Ser Gln Thr Pro Gly Pro Val Val Asp  
 13380 13385 13390  
 Leu Lys Val Arg Ser Val Ser Lys Ser Ser Cys Ser Ile Gly Trp Lys  
 13395 13400 13405  
 Lys Pro His Ser Asp Gly Gly Ser Arg Ile Ile Gly Tyr Val Val Asp  
 13410 13415 13420 1  
 Phe Leu Thr Glu Glu Asn Lys Trp Gln Arg Val Met Lys Ser Leu Ser  
 3425 13430 13435 13440  
 Leu Gln Tyr Ser Ala Lys Asp Leu Thr Glu Gly Lys Glu Tyr Thr Phe  
 13445 13450 13455  
 Arg Val Ser Ala Glu Asn Glu Asn Gly Glu Gly Thr Pro Ser Glu Ile  
 13460 13465 13470  
 Thr Val Val Ala Arg Asp Asp Val Val Ala Pro Asp Leu Asp Leu Lys  
 13475 13480 13485  
 Gly Leu Pro Asp Leu Cys Tyr Leu Ala Lys Glu Asn Ser Asn Phe Arg  
 13490 13495 13500 1  
 Leu Lys Ile Pro Ile Lys Gly Lys Pro Ala Pro Ser Val Ser Trp Lys  
 3505 13510 13515 13520  
 Lys Gly Glu Asp Pro Leu Ala Thr Asp Thr Arg Val Ser Val Glu Ser  
 13525 13530 13535  
 Ser Ala Val Asn Thr Thr Leu Ile Val Tyr Asp Cys Gln Lys Ser Asp  
 13540 13545 13550  
 Ala Gly Lys Tyr Thr Ile Thr Leu Lys Asn Val Ala Gly Thr Lys Glu  
 13555 13560 13565  
 Gly Thr Ile Ser Ile Lys Val Val Gly Lys Pro Gly Ile Pro Thr Gly  
 13570 13575 13580 1  
 Pro Ile Lys Phe Asp Glu Val Thr Ala Glu Ala Met Thr Leu Lys Trp  
 3585 13590 13595 13600  
 Ala Pro Pro Lys Asp Asp Gly Gly Ser Glu Ile Thr Asn Tyr Ile Leu  
 13605 13610 13615

Glu Lys Arg Asp Ser Val Asn Asn Lys Trp Val Thr Cys Ala Ser Ala  
 13620 13625 13630  
 Val Gln Lys Thr Thr Phe Arg Val Thr Arg Leu His Glu Gly Met Glu  
 13635 13640 13645  
 Tyr Thr Phe Arg Val Ser Ala Glu Asn Lys Tyr Gly Val Gly Glu Gly  
 13650 13655 13660 1  
 Leu Lys Ser Glu Pro Ile Val Ala Arg His Pro Phe Asp Val Pro Asp  
 3665 13670 13675 13680  
 Ala Pro Pro Pro Pro Asn Ile Val Asp Val Arg His Asp Ser Val Ser  
 13685 13690 13695  
 Leu Thr Trp Thr Asp Pro Lys Lys Thr Gly Gly Ser Pro Ile Thr Gly  
 13700 13705 13710  
 Tyr His Leu Glu Phe Lys Glu Arg Asn Ser Leu Leu Trp Lys Arg Ala  
 13715 13720 13725  
 Asn Lys Thr Pro Ile Arg Met Arg Asp Phe Lys Val Thr Gly Leu Thr  
 13730 13735 13740 1  
 Glu Gly Leu Glu Tyr Glu Phe Arg Val Met Ala Ile Asn Leu Ala Gly  
 3745 13750 13755 13760  
 Val Gly Lys Pro Ser Leu Pro Ser Glu Pro Val Val Ala Leu Asp Pro  
 13765 13770 13775  
 Ile Asp Pro Pro Gly Lys Pro Glu Val Ile Asn Ile Thr Arg Asn Ser  
 13780 13785 13790  
 Val Thr Leu Ile Trp Thr Glu Pro Lys Tyr Asp Gly Gly His Lys Leu  
 13795 13800 13805  
 Thr Gly Tyr Ile Val Glu Lys Arg Asp Leu Pro Ser Lys Ser Trp Met  
 13810 13815 13820 1  
 Lys Ala Asn His Val Asn Val Pro Glu Cys Ala Phe Thr Val Thr Asp  
 3825 13830 13835 13840  
 Leu Val Glu Gly Gly Lys Tyr Glu Phe Arg Ile Arg Ala Lys Asn Thr  
 13845 13850 13855  
 Ala Gly Ala Ile Ser Ala Pro Ser Glu Ser Thr Glu Thr Ile Ile Cys  
 13860 13865 13870  
 Lys Asp Glu Tyr Glu Ala Pro Thr Ile Val Leu Asp Pro Thr Ile Lys  
 13875 13880 13885  
 Asp Gly Leu Thr Ile Lys Ala Gly Asp Thr Ile Val Leu Asn Ala Ile  
 13890 13895 13900 1  
 Ser Ile Leu Gly Lys Pro Leu Pro Lys Ser Ser Trp Ser Lys Ala Gly  
 3905 13910 13915 13920  
 Lys Asp Ile Arg Pro Ser Asp Ile Thr Gln Ile Thr Ser Thr Pro Thr  
 13925 13930 13935  
 Ser Ser Met Leu Thr Ile Lys Tyr Ala Thr Arg Lys Asp Ala Gly Glu  
 13940 13945 13950  
 Tyr Thr Ile Thr Ala Thr Asn Pro Phe Gly Thr Lys Val Glu His Val  
 13955 13960 13965  
 Lys Val Thr Val Leu Asp Val Pro Gly Pro Pro Gly Pro Val Glu Ile  
 13970 13975 13980 1  
 Ser Asn Val Ser Ala Glu Lys Ala Thr Leu Thr Trp Thr Pro Pro Leu  
 3985 13990 13995 14000  
 Glu Asp Gly Gly Ser Pro Ile Lys Ser Tyr Ile Leu Glu Lys Arg Glu  
 14005 14010 14015  
 Thr Ser Arg Leu Leu Trp Thr Val Val Ser Glu Asp Ile Gln Ser Cys  
 14020 14025 14030  
 Arg His Val Ala Thr Lys Leu Ile Gln Gly Asn Glu Tyr Ile Phe Arg  
 14035 14040 14045  
 Val Ser Ala Val Asn His Tyr Gly Lys Gly Glu Pro Val Gln Ser Glu  
 14050 14055 14060 1  
 Pro Val Lys Met Val Asp Arg Phe Gly Pro Pro Gly Pro Pro Glu Lys  
 4065 14070 14075 14080  
 Pro Glu Val Ser Asn Val Thr Lys Asn Thr Ala Thr Val Ser Trp Lys  
 14085 14090 14095  
 Arg Pro Val Asp Asp Gly Gly Ser Glu Ile Thr Gly Tyr His Val Glu  
 14100 14105 14110

Arg Arg Glu Lys Lys Ser Leu Arg Trp Val Arg Ala Ile Lys Thr Pro  
 14115 14120 14125  
 Val Ser Asp Leu Arg Cys Lys Val Thr Gly Leu Gln Glu Gly Ser Thr  
 14130 14135 14140 1  
 Tyr Glu Phe Arg Val Ser Ala Glu Asn Arg Ala Gly Ile Gly Pro Pro  
 4145 14150 14155 14160  
 Ser Glu Ala Ser Asp Ser Val Leu Met Lys Asp Ala Ala Tyr Pro Pro  
 14165 14170 14175  
 Gly Pro Pro Ser Asn Pro His Val Thr Asp Thr Thr Lys Lys Ser Ala  
 14180 14185 14190  
 Ser Leu Ala Trp Gly Lys Pro His Tyr Asp Gly Gly Leu Glu Ile Thr  
 14195 14200 14205  
 Gly Tyr Val Val Glu His Gln Lys Val Gly Asp Glu Ala Trp Ile Lys  
 14210 14215 14220 1  
 Asp Thr Thr Gly Thr Ala Leu Arg Ile Thr Gln Phe Val Val Pro Asp  
 4225 14230 14235 14240  
 Leu Gln Thr Lys Glu Lys Tyr Asn Phe Arg Ile Ser Ala Ile Asn Asp  
 14245 14250 14255  
 Ala Gly Val Gly Glu Pro Ala Val Ile Pro Asp Val Glu Ile Val Glu  
 14260 14265 14270  
 Arg Glu Met Ala Pro Asp Phe Glu Leu Asp Ala Glu Leu Arg Arg Thr  
 14275 14280 14285  
 Leu Val Val Arg Ala Gly Leu Ser Ile Arg Ile Phe Val Pro Ile Lys  
 14290 14295 14300 1  
 Gly Arg Pro Ala Pro Glu Val Thr Trp Thr Lys Asp Asn Ile Asn Leu  
 4305 14310 14315 14320  
 Lys Asn Arg Ala Asn Ile Glu Asn Thr Glu Ser Phe Thr Leu Leu Ile  
 14325 14330 14335  
 Ile Pro Glu Cys Asn Arg Tyr Asp Thr Gly Lys Phe Val Met Thr Ile  
 14340 14345 14350  
 Glu Asn Pro Ala Gly Lys Lys Ser Gly Phe Val Asn Val Arg Val Leu  
 14355 14360 14365  
 Asp Thr Pro Gly Pro Val Leu Asn Leu Arg Pro Thr Asp Ile Thr Lys  
 14370 14375 14380 1  
 Asp Ser Val Thr Leu His Trp Asp Leu Pro Leu Ile Asp Gly Gly Ser  
 4385 14390 14395 14400  
 Arg Ile Thr Asn Tyr Ile Val Glu Lys Arg Glu Ala Thr Arg Lys Ser  
 14405 14410 14415  
 Tyr Ser Thr Ala Thr Thr Lys Cys His Lys Cys Thr Tyr Lys Val Thr  
 14420 14425 14430  
 Gly Leu Ser Glu Gly Cys Glu Tyr Phe Phe Arg Val Met Ala Glu Asn  
 14435 14440 14445  
 Glu Tyr Gly Ile Gly Glu Pro Thr Glu Thr Thr Glu Pro Val Lys Ala  
 14450 14455 14460 1  
 Ser Glu Ala Pro Ser Pro Pro Asp Ser Leu Asn Ile Met Asp Ile Thr  
 4465 14470 14475 14480  
 Lys Ser Thr Val Ser Leu Ala Trp Pro Lys Pro Lys His Asp Gly Gly  
 14485 14490 14495  
 Ser Lys Ile Thr Gly Tyr Val Ile Glu Ala Gln Arg Lys Gly Ser Asp  
 14500 14505 14510  
 Gln Trp Thr His Ile Thr Thr Val Lys Gly Leu Glu Cys Val Val Arg  
 14515 14520 14525  
 Asn Leu Thr Glu Gly Glu Glu Tyr Thr Phe Gln Val Met Ala Val Asn  
 14530 14535 14540 1  
 Ser Ala Gly Arg Ser Ala Pro Arg Glu Ser Arg Pro Val Ile Val Lys  
 4545 14550 14555 14560  
 Glu Gln Thr Met Leu Pro Glu Leu Asp Leu Arg Gly Ile Tyr Gln Lys  
 14565 14570 14575  
 Leu Val Ile Ala Lys Ala Gly Asp Asn Ile Lys Val Glu Ile Pro Val  
 14580 14585 14590  
 Leu Gly Arg Pro Lys Pro Thr Val Thr Trp Lys Lys Gly Asp Gln Ile  
 14595 14600 14605

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Leu Lys Gln Thr Gln Arg Val Asn Phe Glu Thr Thr Ala Thr Ser Thr
14610                14615                14620                1
Ile Leu Asn Ile Asn Glu Cys Val Arg Ser Asp Ser Gly Pro Tyr Pro
4625                14630                14635                14640
Leu Thr Ala Arg Asn Ile Val Gly Glu Val Gly Asp Val Ile Thr Ile
14645                14650                14655
Gln Val His Asp Ile Pro Gly Pro Pro Thr Gly Pro Ile Lys Phe Asp
14660                14665                14670
Glu Val Ser Ser Asp Phe Val Thr Phe Ser Trp Asp Pro Pro Glu Asn
14675                14680                14685
Asp Gly Gly Val Pro Ile Ser Asn Tyr Val Val Glu Met Arg Gln Thr
14690                14695                14700                1
Asp Ser Thr Thr Trp Val Glu Leu Ala Thr Thr Val Ile Arg Thr Thr
4705                14710                14715                14720
Tyr Lys Ala Thr Arg Leu Thr Thr Gly Leu Glu Tyr Gln Phe Arg Val
14725                14730                14735
Lys Ala Gln Asn Arg Tyr Gly Val Gly Pro Gly Ile Thr Ser Ala Trp
14740                14745                14750
Ile Val Ala Asn Tyr Pro Phe Lys Val Pro Gly Pro Pro Gly Thr Pro
14755                14760                14765
Gln Val Thr Ala Val Thr Lys Asp Ser Met Thr Ile Ser Trp His Glu
14770                14775                14780                1
Pro Leu Ser Asp Gly Gly Ser Pro Ile Leu Gly Tyr His Val Glu Arg
4785                14790                14795                14800
Lys Glu Arg Asn Gly Ile Leu Trp Gln Thr Val Ser Lys Ala Leu Val
14805                14810                14815
Pro Gly Asn Ile Phe Lys Ser Ser Gly Leu Thr Asp Gly Ile Ala Tyr
14820                14825                14830
Glu Phe Arg Val Ile Ala Glu Asn Met Ala Gly Lys Ser Lys Pro Ser
14835                14840                14845
Lys Pro Ser Glu Pro Met Leu Ala Leu Asp Pro Ile Asp Pro Pro Gly
14850                14855                14860                1
Lys Pro Val Pro Leu Asn Ile Thr Arg His Thr Val Thr Leu Lys Trp
4865                14870                14875                14880
Ala Lys Pro Glu Tyr Thr Gly Gly Phe Lys Ile Thr Ser Tyr Ile Val
14885                14890                14895
Glu Lys Arg Asp Leu Pro Asn Gly Arg Trp Leu Lys Ala Asn Phe Ser
14900                14905                14910
Asn Ile Leu Glu Asn Glu Phe Thr Val Ser Gly Leu Thr Glu Asp Ala
14915                14920                14925
Ala Tyr Glu Phe Arg Val Ile Ala Lys Asn Ala Ala Gly Ala Ile Ser
14930                14935                14940                1
Pro Pro Ser Glu Pro Ser Asp Ala Ile Thr Cys Arg Asp Asp Val Glu
4945                14950                14955                14960
Ala Pro Lys Ile Lys Val Asp Val Lys Phe Lys Asp Thr Val Ile Leu
14965                14970                14975
Lys Ala Gly Glu Ala Phe Arg Leu Glu Ala Asp Val Ser Gly Arg Pro
14980                14985                14990
Pro Pro Thr Met Glu Trp Ser Lys Asp Gly Lys Glu Leu Glu Gly Thr
14995                15000                15005
Ala Lys Leu Glu Ile Lys Ile Ala Asp Phe Ser Thr Asn Leu Val Asn
15010                15015                15020                1
Lys Asp Ser Thr Arg Arg Asp Ser Gly Ala Tyr Thr Leu Thr Ala Thr
5025                15030                15035                15040
Asn Pro Gly Gly Phe Ala Lys His Ile Phe Asn Val Lys Val Leu Asp
15045                15050                15055
Arg Pro Gly Pro Pro Glu Gly Pro Leu Ala Val Thr Glu Val Thr Ser
15060                15065                15070
Glu Lys Cys Val Leu Ser Trp Phe Pro Pro Leu Asp Asp Gly Gly Ala
15075                15080                15085
Lys Ile Asp His Tyr Ile Val Gln Lys Arg Glu Thr Ser Arg Leu Ala
15090                15095                15100                1

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Trp Thr Asn Val Ala Ser Glu Val Gln Val Thr Lys Leu Lys Val Thr  
 5105 15110 15115 15120  
 Lys Leu Leu Lys Gly Asn Glu Tyr Ile Phe Arg Val Met Ala Val Asn  
 15125 15130 15135  
 Lys Tyr Gly Val Gly Glu Pro Leu Glu Ser Glu Pro Val Leu Ala Val  
 15140 15145 15150  
 Asn Pro Tyr Gly Pro Pro Asp Pro Pro Lys Asn Pro Glu Val Thr Thr  
 15155 15160 15165  
 Ile Thr Lys Asp Ser Met Val Val Cys Trp Gly His Pro Asp Ser Asp  
 15170 15175 15180 1  
 Gly Gly Ser Glu Ile Ile Asn Tyr Ile Val Glu Arg Arg Asp Lys Ala  
 5185 15190 15195 15200  
 Gly Gln Arg Trp Ile Lys Cys Asn Lys Lys Thr Leu Thr Asp Leu Arg  
 15205 15210 15215  
 Tyr Lys Val Ser Gly Leu Thr Glu Gly His Glu Tyr Glu Phe Arg Ile  
 15220 15225 15230  
 Met Ala Glu Asn Ala Ala Gly Ile Ser Ala Pro Ser Pro Thr Ser Pro  
 15235 15240 15245  
 Phe Tyr Lys Ala Cys Asp Thr Val Phe Lys Pro Gly Pro Pro Gly Asn  
 15250 15255 15260 1  
 Pro Arg Val Leu Asp Thr Ser Arg Ser Ser Ile Ser Ile Ala Trp Asn  
 5265 15270 15275 15280  
 Lys Pro Ile Tyr Asp Gly Gly Ser Glu Ile Thr Gly Tyr Met Val Glu  
 15285 15290 15295  
 Ile Ala Leu Pro Glu Glu Asp Glu Trp Gln Ile Val Thr Pro Pro Ala  
 15300 15305 15310  
 Gly Leu Lys Ala Thr Ser Tyr Thr Ile Thr Gly Leu Thr Glu Asn Gln  
 15315 15320 15325  
 Glu Tyr Lys Ile Arg Ile Tyr Ala Met Asn Ser Glu Gly Leu Gly Glu  
 15330 15335 15340 1  
 Pro Ala Leu Val Pro Gly Thr Pro Lys Ala Glu Asp Arg Met Leu Pro  
 5345 15350 15355 15360  
 Pro Glu Ile Glu Leu Asp Ala Asp Leu Arg Lys Val Val Thr Ile Arg  
 15365 15370 15375  
 Ala Cys Cys Thr Leu Arg Leu Phe Val Pro Ile Lys Gly Arg Pro Asp  
 15380 15385 15390  
 Pro Glu Val Lys Trp Ala Arg Asp His Gly Glu Ser Leu Asp Lys Ala  
 15395 15400 15405  
 Ser Ile Glu Ser Ala Ser Ser Tyr Thr Leu Leu Ile Val Gly Asn Val  
 15410 15415 15420 1  
 Asn Arg Phe Asp Ser Gly Lys Tyr Ile Leu Thr Val Glu Asn Ser Ser  
 5425 15430 15435 15440  
 Gly Ser Lys Ser Ala Phe Val Asn Val Arg Val Leu Asp Thr Pro Gly  
 15445 15450 15455  
 Pro Pro Gln Asp Leu Lys Val Lys Glu Val Thr Lys Thr Ser Val Thr  
 15460 15465 15470  
 Leu Thr Trp Asp Pro Pro Leu Leu Asp Gly Gly Ser Lys Ile Lys Asn  
 15475 15480 15485  
 Tyr Ile Val Glu Lys Arg Glu Ser Thr Arg Lys Ala Tyr Ser Thr Val  
 15490 15495 15500 1  
 Ala Thr Asn Cys His Lys Thr Ser Trp Lys Val Asp Gln Leu Gln Glu  
 5505 15510 15515 15520  
 Gly Cys Ser Tyr Tyr Phe Arg Val Leu Ala Glu Asn Glu Tyr Gly Ile  
 15525 15530 15535  
 Gly Leu Pro Ala Glu Thr Ala Glu Ser Val Lys Ala Ser Glu Arg Pro  
 15540 15545 15550  
 Leu Pro Pro Gly Lys Ile Thr Leu Met Asp Val Thr Arg Asn Ser Val  
 15555 15560 15565  
 Ser Leu Ser Trp Glu Lys Pro Glu His Asp Gly Gly Ser Arg Ile Leu  
 15570 15575 15580 1  
 Gly Tyr Ile Val Glu Met Gln Thr Lys Gly Ser Asp Lys Trp Ala Thr  
 5585 15590 15595 15600



Cys Ala Thr Val Lys Val Thr Glu Ala Thr Ile Thr Gly Leu Ile Gln  
 15605 15610 15615  
 Gly Glu Glu Tyr Ser Phe Arg Val Ser Ala Gln Asn Glu Lys Gly Ile  
 15620 15625 15630  
 Ser Asp Pro Arg Gln Leu Ser Val Pro Val Ile Ala Lys Asp Leu Val  
 15635 15640 15645  
 Ile Pro Pro Ala Phe Lys Leu Leu Phe Asn Thr Phe Thr Val Leu Ala  
 15650 15655 15660 1  
 Gly Glu Asp Leu Lys Val Asp Val Pro Phe Ile Gly Arg Pro Thr Pro  
 5665 15670 15675 15680  
 Ala Val Thr Trp His Lys Asp Asn Val Pro Leu Lys Gln Thr Thr Arg  
 15685 15690 15695  
 Val Asn Ala Glu Ser Thr Glu Asn Asn Ser Leu Leu Thr Ile Lys Asp  
 15700 15705 15710  
 Ala Cys Arg Glu Asp Val Gly His Tyr Val Val Lys Leu Thr Asn Ser  
 15715 15720 15725  
 Ala Gly Glu Ala Ile Glu Thr Leu Asn Val Ile Val Leu Asp Lys Pro  
 15730 15735 15740 1  
 Gly Pro Pro Thr Gly Pro Val Lys Met Asp Glu Val Thr Ala Asp Ser  
 5745 15750 15755 15760  
 Ile Thr Leu Ser Trp Gly Pro Pro Lys Tyr Asp Gly Gly Ser Ser Ile  
 15765 15770 15775  
 Asn Asn Tyr Ile Val Glu Lys Arg Asp Thr Ser Thr Thr Thr Trp Gln  
 15780 15785 15790  
 Ile Val Ser Ala Thr Val Ala Arg Thr Thr Ile Lys Ala Cys Arg Leu  
 15795 15800 15805  
 Lys Thr Gly Cys Glu Tyr Gln Phe Arg Ile Ala Ala Glu Asn Arg Tyr  
 15810 15815 15820 1  
 Gly Lys Ser Thr Tyr Leu Asn Ser Glu Pro Thr Val Ala Gln Tyr Pro  
 5825 15830 15835 15840  
 Phe Lys Val Pro Gly Pro Pro Gly Thr Pro Val Val Thr Leu Ser Ser  
 15845 15850 15855  
 Arg Asp Ser Met Glu Val Gln Trp Asn Glu Pro Ile Ser Asp Gly Gly  
 15860 15865 15870  
 Ser Arg Val Ile Gly Tyr His Leu Glu Arg Lys Glu Arg Asn Ser Ile  
 15875 15880 15885  
 Leu Trp Val Lys Leu Asn Lys Thr Pro Ile Pro Gln Thr Lys Phe Lys  
 15890 15895 15900 1  
 Thr Thr Gly Leu Glu Glu Gly Val Glu Tyr Glu Phe Arg Val Ser Ala  
 5905 15910 15915 15920  
 Glu Asn Ile Val Gly Ile Gly Lys Pro Ser Lys Val Ser Glu Cys Tyr  
 15925 15930 15935  
 Val Ala Arg Asp Pro Cys Asp Pro Pro Gly Arg Pro Glu Ala Ile Ile  
 15940 15945 15950  
 Val Thr Arg Asn Ser Val Thr Leu Gln Trp Lys Lys Pro Thr Tyr Asp  
 15955 15960 15965  
 Gly Gly Ser Lys Ile Thr Gly Tyr Ile Val Glu Lys Lys Glu Leu Pro  
 15970 15975 15980 1  
 Glu Gly Arg Trp Met Lys Ala Ser Phe Thr Asn Ile Ile Asp Thr His  
 5985 15990 15995 16000  
 Phe Glu Val Thr Gly Leu Val Glu Asp His Arg Tyr Glu Phe Arg Val  
 16005 16010 16015  
 Ile Ala Arg Asn Ala Ala Gly Val Phe Ser Glu Pro Ser Glu Ser Thr  
 16020 16025 16030  
 Gly Ala Ile Thr Ala Arg Asp Glu Val Asp Pro Pro Arg Ile Ser Met  
 16035 16040 16045  
 Asp Pro Lys Tyr Lys Asp Thr Ile Val Val His Ala Gly Glu Ser Phe  
 16050 16055 16060 1  
 Lys Val Asp Ala Asp Ile Tyr Gly Lys Pro Ile Pro Thr Ile Gln Trp  
 6065 16070 16075 16080  
 Ile Lys Gly Asp Gln Glu Leu Ser Asn Thr Ala Arg Leu Glu Ile Lys  
 16085 16090 16095

Ser Thr Asp Phe Ala Thr Ser Leu Ser Val Lys Asp Ala Val Arg Val  
 16100 16105 16110  
 Asp Ser Gly Asn Tyr Ile Leu Lys Ala Lys Asn Val Ala Gly Glu Arg  
 16115 16120 16125  
 Ser Val Thr Val Asn Val Lys Val Leu Asp Arg Pro Gly Pro Pro Glu  
 16130 16135 16140 1  
 Gly Pro Val Val Ile Ser Gly Val Thr Ala Glu Lys Cys Thr Leu Ala  
 6145 16150 16155 16160  
 Trp Lys Pro Pro Leu Gln Asp Gly Gly Ser Asp Ile Ile Asn Tyr Ile  
 16165 16170 16175  
 Val Glu Arg Arg Glu Thr Ser Arg Leu Val Trp Thr Val Val Asp Ala  
 16180 16185 16190  
 Asn Val Gln Thr Leu Ser Cys Lys Val Thr Lys Leu Leu Glu Gly Asn  
 16195 16200 16205  
 Glu Tyr Thr Phe Arg Ile Met Ala Val Asn Lys Tyr Gly Val Gly Glu  
 16210 16215 16220 1  
 Pro Leu Glu Ser Glu Pro Val Val Ala Lys Asn Pro Phe Val Val Pro  
 6225 16230 16235 16240  
 Asp Ala Pro Lys Ala Pro Glu Val Thr Thr Val Thr Lys Asp Ser Met  
 16245 16250 16255  
 Ile Val Val Trp Glu Arg Pro Ala Ser Asp Gly Gly Ser Glu Ile Leu  
 16260 16265 16270  
 Gly Tyr Val Leu Glu Lys Arg Asp Lys Glu Gly Ile Arg Trp Thr Arg  
 16275 16280 16285  
 Cys His Lys Arg Leu Ile Gly Glu Leu Arg Leu Arg Val Thr Gly Leu  
 16290 16295 16300 1  
 Ile Glu Asn His Asp Tyr Glu Phe Arg Val Ser Ala Glu Asn Ala Ala  
 6305 16310 16315 16320  
 Gly Leu Ser Glu Pro Ser Pro Pro Ser Ala Tyr Gln Lys Ala Cys Asp  
 16325 16330 16335  
 Pro Ile Tyr Lys Pro Gly Pro Pro Asn Asn Pro Lys Val Ile Asp Ile  
 16340 16345 16350  
 Thr Arg Ser Ser Val Phe Leu Ser Trp Ser Lys Pro Ile Tyr Asp Gly  
 16355 16360 16365  
 Gly Cys Glu Ile Gln Gly Tyr Ile Val Glu Lys Cys Asp Val Asn Val  
 16370 16375 16380 1  
 Gly Glu Trp Thr Met Cys Thr Pro Pro Thr Gly Ile Asn Lys Thr Asn  
 6385 16390 16395 16400  
 Ile Glu Val Glu Lys Leu Leu Glu Lys His Glu Tyr Asn Phe Arg Ile  
 16405 16410 16415  
 Cys Ala Ile Asn Lys Ala Gly Val Gly Glu His Ala Asp Val Pro Gly  
 16420 16425 16430  
 Pro Ile Ile Val Glu Glu Lys Leu Glu Ala Pro Asp Ile Asp Leu Asp  
 16435 16440 16445  
 Leu Glu Leu Arg Lys Ile Ile Asn Ile Arg Ala Gly Gly Ser Leu Arg  
 16450 16455 16460 1  
 Leu Phe Val Pro Ile Lys Gly Arg Pro Thr Pro Glu Val Lys Trp Gly  
 6465 16470 16475 16480  
 Lys Val Asp Gly Glu Ile Arg Asp Ala Ala Ile Ile Asp Val Thr Ser  
 16485 16490 16495  
 Ser Phe Thr Ser Leu Val Leu Asp Asn Val Asn Arg Tyr Asp Ser Gly  
 16500 16505 16510  
 Lys Tyr Thr Leu Thr Leu Glu Asn Ser Ser Gly Thr Lys Ser Ala Phe  
 16515 16520 16525  
 Val Thr Val Arg Val Leu Asp Thr Pro Ser Pro Pro Val Asn Leu Lys  
 16530 16535 16540 1  
 Val Thr Glu Ile Thr Lys Asp Ser Val Ser Ile Thr Trp Glu Pro Pro  
 6545 16550 16555 16560  
 Leu Leu Asp Gly Gly Ser Lys Ile Lys Asn Tyr Ile Val Glu Lys Arg  
 16565 16570 16575  
 Glu Ala Thr Arg Lys Ser Tyr Ala Ala Val Val Thr Asn Cys His Lys  
 16580 16585 16590

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Asn Ser Trp Lys Ile Asp Gln Leu Gln Glu Gly Cys Ser Tyr Tyr Phe
  16595                16600                16605
Arg Val Thr Ala Glu Asn Glu Tyr Gly Ile Gly Leu Pro Ala Gln Thr
  16610                16615                16620                1
Ala Asp Pro Ile Lys Val Ala Glu Val Pro Gln Pro Pro Gly Lys Ile
  6625                16630                16635                16640
Thr Val Asp Asp Val Thr Arg Asn Ser Val Ser Leu Ser Trp Thr Lys
  16645                16650                16655
Pro Glu His Asp Gly Gly Ser Lys Ile Ile Gln Tyr Ile Val Glu Met
  16660                16665                16670
Gln Ala Lys His Ser Glu Lys Trp Ser Glu Cys Ala Arg Val Lys Ser
  16675                16680                16685
Leu Gln Ala Val Ile Thr Asn Leu Thr Gln Gly Glu Glu Tyr Leu Phe
  16690                16695                16700                1
Arg Val Val Ala Val Asn Glu Lys Gly Arg Ser Asp Pro Arg Ser Leu
  6705                16710                16715                16720
Ala Val Pro Ile Val Ala Lys Asp Leu Val Ile Glu Pro Asp Val Lys
  16725                16730                16735
Pro Ala Phe Ser Ser Tyr Ser Val Gln Val Gly Gln Asp Leu Lys Ile
  16740                16745                16750
Glu Val Pro Ile Ser Gly Arg Pro Lys Pro Thr Ile Thr Trp Thr Lys
  16755                16760                16765
Asp Gly Leu Pro Leu Lys Gln Thr Thr Arg Ile Asn Val Thr Asp Ser
  16770                16775                16780                1
Leu Asp Leu Thr Thr Leu Ser Ile Lys Glu Thr His Lys Asp Asp Gly
  6785                16790                16795                16800
Gly Gln Tyr Gly Ile Thr Val Ala Asn Val Val Gly Gln Lys Thr Ala
  16805                16810                16815
Ser Ile Glu Ile Val Thr Leu Asp Lys Pro Asp Pro Pro Lys Gly Pro
  16820                16825                16830
Val Lys Phe Asp Asp Val Ser Ala Glu Ser Ile Thr Leu Ser Trp Asn
  16835                16840                16845
Pro Pro Leu Tyr Thr Gly Gly Cys Gln Ile Thr Asn Tyr Ile Val Gln
  16850                16855                16860                1
Lys Arg Asp Thr Thr Thr Thr Val Trp Asp Val Val Ser Ala Thr Val
  6865                16870                16875                16880
Ala Arg Thr Thr Leu Lys Val Thr Lys Leu Lys Thr Gly Thr Glu Tyr
  16885                16890                16895
Gln Phe Arg Ile Phe Ala Glu Asn Arg Tyr Gly Gln Ser Phe Ala Leu
  16900                16905                16910
Glu Ser Asp Pro Ile Val Ala Gln Tyr Pro Tyr Lys Glu Pro Gly Pro
  16915                16920                16925
Pro Gly Thr Pro Phe Ala Thr Ala Ile Ser Lys Asp Ser Met Val Ile
  16930                16935                16940                1
Gln Trp His Glu Pro Val Asn Asn Gly Gly Ser Pro Val Ile Gly Tyr
  6945                16950                16955                16960
His Leu Glu Arg Lys Glu Arg Asn Ser Ile Leu Trp Thr Lys Val Asn
  16965                16970                16975
Lys Thr Ile Ile His Asp Thr Gln Phe Lys Ala Gln Asn Leu Glu Glu
  16980                16985                16990
Gly Ile Glu Tyr Glu Phe Arg Val Tyr Ala Glu Asn Ile Val Gly Val
  16995                17000                17005
Gly Lys Ala Ser Lys Asn Ser Glu Cys Tyr Val Ala Arg Asp Pro Cys
  17010                17015                17020                1
Asp Pro Pro Gly Thr Pro Glu Pro Ile Met Val Lys Arg Asn Glu Ile
  7025                17030                17035                17040
Thr Leu Gln Trp Thr Lys Pro Val Tyr Asp Gly Gly Ser Met Ile Thr
  17045                17050                17055
Gly Tyr Ile Val Glu Lys Arg Asp Leu Pro Asp Gly Arg Trp Met Lys
  17060                17065                17070
Ala Ser Phe Thr Asn Val Ile Glu Thr Gln Phe Thr Val Ser Gly Leu
  17075                17080                17085

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Thr Glu Asp Gln Arg Tyr Glu Phe Arg Val Ile Ala Lys Asn Ala Ala  
 17090 17095 17100 1  
 Gly Ala Ile Ser Lys Pro Ser Asp Ser Thr Gly Pro Ile Thr Ala Lys  
 7105 17110 17115 17120  
 Asp Glu Val Glu Leu Pro Arg Ile Ser Met Asp Pro Lys Phe Arg Asp  
 17125 17130 17135  
 Thr Ile Val Val Asn Ala Gly Glu Thr Phe Arg Leu Glu Ala Asp Val  
 17140 17145 17150  
 His Gly Lys Pro Leu Pro Thr Ile Glu Trp Leu Arg Gly Asp Lys Glu  
 17155 17160 17165  
 Ile Glu Glu Ser Ala Arg Cys Glu Ile Lys Asn Thr Asp Phe Lys Ala  
 17170 17175 17180 1  
 Leu Leu Ile Val Lys Asp Ala Ile Arg Ile Asp Gly Gly Gln Tyr Ile  
 7185 17190 17195 17200  
 Leu Arg Ala Ser Asn Val Ala Gly Ser Lys Ser Phe Pro Val Asn Val  
 17205 17210 17215  
 Lys Val Leu Asp Arg Pro Gly Pro Pro Glu Gly Pro Val Gln Val Thr  
 17220 17225 17230  
 Gly Val Thr Ser Glu Lys Cys Ser Leu Thr Trp Ser Pro Pro Leu Gln  
 17235 17240 17245  
 Asp Gly Gly Ser Asp Ile Ser His Tyr Val Val Glu Lys Arg Glu Thr  
 17250 17255 17260 1  
 Ser Arg Leu Ala Trp Thr Val Val Ala Ser Glu Val Val Thr Asn Ser  
 7265 17270 17275 17280  
 Leu Lys Val Thr Lys Leu Leu Glu Gly Asn Glu Tyr Val Phe Arg Ile  
 17285 17290 17295  
 Met Ala Val Asn Lys Tyr Gly Val Gly Glu Pro Leu Glu Ser Ala Pro  
 17300 17305 17310  
 Val Leu Met Lys Asn Pro Phe Val Leu Pro Gly Pro Pro Lys Ser Leu  
 17315 17320 17325  
 Glu Val Thr Asn Ile Ala Lys Asp Ser Met Thr Val Cys Trp Asn Arg  
 17330 17335 17340 1  
 Pro Asp Ser Asp Gly Gly Ser Glu Ile Ile Gly Tyr Ile Val Glu Lys  
 7345 17350 17355 17360  
 Arg Asp Arg Ser Gly Ile Arg Trp Ile Lys Cys Asn Lys Arg Arg Ile  
 17365 17370 17375  
 Thr Asp Leu Arg Leu Arg Val Thr Gly Leu Thr Glu Asp His Glu Tyr  
 17380 17385 17390  
 Glu Phe Arg Val Ser Ala Glu Asn Ala Ala Gly Val Gly Glu Pro Ser  
 17395 17400 17405  
 Pro Ala Thr Val Tyr Tyr Lys Ala Cys Asp Pro Val Phe Lys Pro Gly  
 17410 17415 17420 1  
 Pro Pro Thr Asn Ala His Ile Val Asp Thr Thr Lys Asn Ser Ile Thr  
 7425 17430 17435 17440  
 Leu Ala Trp Gly Lys Pro Ile Tyr Asp Gly Gly Ser Glu Ile Leu Gly  
 17445 17450 17455  
 Tyr Val Val Glu Ile Cys Lys Ala Asp Glu Glu Glu Trp Gln Ile Val  
 17460 17465 17470  
 Thr Pro Gln Thr Gly Leu Arg Val Thr Arg Phe Glu Ile Ser Lys Leu  
 17475 17480 17485  
 Thr Glu His Gln Glu Tyr Lys Ile Arg Val Cys Ala Leu Asn Lys Val  
 17490 17495 17500 1  
 Gly Leu Gly Glu Ala Thr Ser Val Pro Gly Thr Val Lys Pro Glu Asp  
 7505 17510 17515 17520  
 Lys Leu Glu Ala Pro Glu Leu Asp Leu Asp Ser Glu Leu Arg Lys Gly  
 17525 17530 17535  
 Ile Val Val Arg Ala Gly Gly Ser Ala Arg Ile His Ile Pro Phe Lys  
 17540 17545 17550  
 Gly Arg Pro Met Pro Glu Ile Thr Trp Ser Arg Glu Glu Gly Glu Phe  
 17555 17560 17565  
 Thr Asp Lys Val Gln Ile Glu Lys Gly Val Asn Tyr Thr Gln Leu Ser  
 17570 17575 17580 1

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Ile Asp Asn Cys Asp Arg Asn Asp Ala Gly Lys Tyr Ile Leu Lys Leu
7585          17590          17595          17600
Glu Asn Ser Ser Gly Ser Lys Ser Ala Phe Val Thr Val Lys Val Leu
          17605          17610          17615
Asp Thr Pro Gly Pro Pro Gln Asn Leu Ala Val Lys Glu Val Arg Lys
          17620          17625          17630
Asp Ser Ala Phe Leu Val Trp Glu Pro Pro Ile Ile Asp Gly Gly Ala
          17635          17640          17645
Lys Val Lys Asn Tyr Val Ile Asp Lys Arg Glu Ser Thr Arg Lys Ala
          17650          17655          17660          1
Tyr Ala Asn Val Ser Ser Lys Cys Ser Lys Thr Ser Phe Lys Val Glu
7665          17670          17675          17680
Asn Leu Thr Glu Gly Ala Ile Tyr Tyr Phe Arg Val Met Ala Glu Asn
          17685          17690          17695
Glu Phe Gly Val Gly Val Pro Val Glu Thr Val Asp Ala Val Lys Ala
          17700          17705          17710
Ala Glu Pro Pro Ser Pro Pro Gly Lys Val Thr Leu Thr Asp Val Ser
          17715          17720          17725
Gln Thr Ser Ala Ser Leu Met Trp Glu Lys Pro Glu His Asp Gly Gly
          17730          17735          17740          1
Ser Arg Val Leu Gly Tyr Val Val Glu Met Gln Pro Lys Gly Thr Glu
7745          17750          17755          17760
Lys Trp Ser Ile Val Ala Glu Ser Lys Val Cys Asn Ala Val Val Thr
          17765          17770          17775
Gly Leu Ser Ser Gly Gln Glu Tyr Gln Phe Arg Val Lys Ala Tyr Asn
          17780          17785          17790
Glu Lys Gly Lys Ser Asp Pro Arg Val Leu Gly Val Pro Val Ile Ala
          17795          17800          17805
Lys Asp Leu Thr Ile Gln Pro Ser Leu Lys Leu Pro Phe Asn Thr Tyr
          17810          17815          17820          1
Ser Ile Gln Ala Gly Glu Asp Leu Lys Ile Glu Ile Pro Val Ile Gly
7825          17830          17835          17840
Arg Pro Arg Pro Asn Ile Ser Trp Val Lys Asp Gly Glu Pro Leu Lys
          17845          17850          17855
Gln Thr Thr Arg Val Asn Val Glu Glu Thr Ala Thr Ser Thr Val Leu
          17860          17865          17870
His Ile Lys Glu Gly Asn Lys Asp Asp Phe Gly Lys Tyr Thr Val Thr
          17875          17880          17885
Ala Thr Asn Ser Ala Gly Thr Ala Thr Glu Asn Leu Ser Val Ile Val
          17890          17895          17900          1
Leu Glu Lys Pro Gly Pro Pro Val Gly Pro Val Arg Phe Asp Glu Val
7905          17910          17915          17920
Ser Ala Asp Phe Val Val Ile Ser Trp Glu Pro Pro Ala Tyr Thr Gly
          17925          17930          17935
Gly Cys Gln Ile Ser Asn Tyr Ile Val Glu Lys Arg Asp Thr Thr Thr
          17940          17945          17950
Thr Thr Trp His Met Val Ser Ala Thr Val Ala Arg Thr Thr Ile Lys
          17955          17960          17965
Ile Thr Lys Leu Lys Thr Gly Thr Glu Tyr Gln Phe Arg Ile Phe Ala
          17970          17975          17980          1
Glu Asn Arg Tyr Gly Lys Ser Ala Pro Leu Asp Ser Lys Ala Val Ile
7985          17990          17995          18000
Val Gln Tyr Pro Phe Lys Glu Pro Gly Pro Pro Gly Thr Pro Phe Val
          18005          18010          18015
Thr Ser Ile Ser Lys Asp Gln Met Leu Val Gln Trp His Glu Pro Val
          18020          18025          18030
Asn Asp Gly Gly Thr Lys Ile Ile Gly Tyr His Leu Glu Gln Lys Glu
          18035          18040          18045
Lys Asn Ser Ile Leu Trp Val Lys Leu Asn Lys Thr Pro Ile Gln Asp
          18050          18055          18060          1
Thr Lys Phe Lys Thr Thr Gly Leu Asp Glu Gly Leu Glu Tyr Glu Phe
8065          18070          18075          18080

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Lys Val Ser Ala Glu Asn Ile Val Gly Ile Gly Lys Pro Ser Lys Val  
 18085 18090 18095  
 Ser Glu Cys Phe Val Ala Arg Asp Pro Cys Asp Pro Pro Gly Arg Pro  
 18100 18105 18110  
 Glu Ala Ile Val Ile Thr Arg Asn Asn Val Thr Leu Lys Trp Lys Lys  
 18115 18120 18125  
 Pro Ala Tyr Asp Gly Gly Ser Lys Ile Thr Gly Tyr Ile Val Glu Lys  
 18130 18135 18140 1  
 Lys Asp Leu Pro Asp Gly Arg Trp Met Lys Ala Ser Phe Thr Asn Val  
 8145 18150 18155 18160  
 Leu Glu Thr Glu Phe Thr Val Ser Gly Leu Val Glu Asp Gln Arg Tyr  
 18165 18170 18175  
 Glu Phe Arg Val Ile Ala Arg Asn Ala Ala Gly Asn Phe Ser Glu Pro  
 18180 18185 18190  
 Ser Asp Ser Ser Gly Ala Ile Thr Ala Arg Asp Glu Ile Asp Ala Pro  
 18195 18200 18205  
 Asn Ala Ser Leu Asp Pro Lys Tyr Lys Asp Val Ile Val Val His Ala  
 18210 18215 18220 1  
 Gly Glu Thr Phe Val Leu Glu Ala Asp Ile Arg Gly Lys Pro Ile Pro  
 8225 18230 18235 18240  
 Asp Val Val Trp Ser Lys Asp Gly Lys Glu Leu Glu Glu Thr Ala Ala  
 18245 18250 18255  
 Arg Met Glu Ile Lys Ser Thr Ile Gln Lys Thr Thr Leu Val Val Lys  
 18260 18265 18270  
 Asp Cys Ile Arg Thr Asp Gly Gly Gln Tyr Ile Leu Lys Leu Ser Asn  
 18275 18280 18285  
 Val Gly Gly Thr Lys Ser Ile Pro Ile Thr Val Lys Val Leu Asp Arg  
 18290 18295 18300 1  
 Pro Gly Ser Pro Glu Gly Pro Leu Lys Val Thr Gly Val Thr Ala Glu  
 8305 18310 18315 18320  
 Lys Cys Tyr Leu Ala Trp Asn Pro Pro Leu Gln Asp Gly Gly Ala Asn  
 18325 18330 18335  
 Ile Ser His Tyr Ile Ile Glu Lys Arg Glu Thr Ser Arg Leu Ser Trp  
 18340 18345 18350  
 Thr Gln Val Ser Thr Glu Val Gln Ala Leu Asn Tyr Lys Val Thr Lys  
 18355 18360 18365  
 Leu Leu Pro Gly Asn Glu Tyr Ile Phe Arg Val Met Ala Val Asn Lys  
 18370 18375 18380 1  
 Tyr Gly Ile Gly Glu Pro Leu Glu Ser Gly Pro Val Thr Ala Cys Asn  
 8385 18390 18395 18400  
 Pro Tyr Lys Pro Pro Gly Pro Pro Ser Thr Pro Glu Val Ser Ala Ile  
 18405 18410 18415  
 Thr Lys Asp Ser Met Val Val Thr Trp Ala Arg Pro Val Asp Asp Gly  
 18420 18425 18430  
 Gly Thr Glu Ile Glu Gly Tyr Ile Leu Glu Lys Arg Asp Lys Glu Gly  
 18435 18440 18445  
 Val Arg Trp Thr Lys Cys Asn Lys Lys Thr Leu Thr Asp Leu Arg Leu  
 18450 18455 18460 1  
 Arg Val Thr Gly Leu Thr Glu Gly His Ser Tyr Glu Phe Arg Val Ala  
 8465 18470 18475 18480  
 Ala Glu Asn Ala Ala Gly Val Gly Glu Pro Ser Glu Pro Ser Val Phe  
 18485 18490 18495  
 Tyr Arg Ala Cys Asp Ala Leu Tyr Pro Pro Gly Pro Pro Ser Asn Pro  
 18500 18505 18510  
 Lys Val Thr Asp Thr Ser Arg Ser Ser Val Ser Leu Ala Trp Ser Lys  
 18515 18520 18525  
 Pro Ile Tyr Asp Gly Gly Ala Pro Val Lys Gly Tyr Val Val Glu Val  
 18530 18535 18540 1  
 Lys Glu Ala Ala Ala Asp Glu Trp Thr Thr Cys Thr Pro Pro Thr Gly  
 8545 18550 18555 18560  
 Leu Gln Gly Lys Gln Phe Thr Val Thr Lys Leu Lys Glu Asn Thr Glu  
 18565 18570 18575

Tyr Asn Phe Arg Ile Cys Ala Ile Asn Ser Glu Gly Val Gly Glu Pro  
 18580 18585 18590  
 Ala Thr Leu Pro Gly Ser Val Val Ala Gln Glu Arg Ile Glu Pro Pro  
 18595 18600 18605  
 Glu Ile Glu Leu Asp Ala Asp Leu Arg Lys Val Val Val Leu Arg Ala  
 18610 18615 18620 1  
 Ser Ala Thr Leu Arg Leu Phe Val Thr Ile Lys Gly Arg Pro Glu Pro  
 8625 18630 18635 18640  
 Glu Val Lys Trp Glu Lys Ala Glu Gly Ile Leu Thr Asp Arg Ala Gln  
 18645 18650 18655  
 Ile Glu Val Thr Ser Ser Phe Thr Met Leu Val Ile Asp Asn Val Thr  
 18660 18665 18670  
 Arg Phe Asp Ser Gly Arg Tyr Asn Leu Thr Leu Glu Asn Asn Ser Gly  
 18675 18680 18685  
 Ser Lys Thr Ala Phe Val Asn Val Arg Val Leu Asp Ser Pro Ser Ala  
 18690 18695 18700 1  
 Pro Val Asn Leu Thr Ile Arg Glu Val Lys Lys Asp Ser Val Thr Leu  
 8705 18710 18715 18720  
 Ser Trp Glu Pro Pro Leu Ile Asp Gly Gly Ala Lys Ile Thr Asn Tyr  
 18725 18730 18735  
 Ile Val Glu Lys Arg Glu Thr Thr Arg Lys Ala Tyr Ala Thr Ile Thr  
 18740 18745 18750  
 Asn Asn Cys Thr Lys Thr Thr Phe Arg Ile Glu Asn Leu Gln Glu Gly  
 18755 18760 18765  
 Cys Ser Tyr Tyr Phe Arg Val Leu Ala Ser Asn Glu Tyr Gly Ile Gly  
 18770 18775 18780 1  
 Leu Pro Ala Glu Thr Thr Glu Pro Val Lys Val Ser Glu Pro Pro Leu  
 8785 18790 18795 18800  
 Pro Pro Gly Arg Val Thr Leu Val Asp Val Thr Arg Asn Thr Ala Thr  
 18805 18810 18815  
 Ile Lys Trp Glu Lys Pro Glu Ser Asp Gly Gly Ser Lys Ile Thr Gly  
 18820 18825 18830  
 Tyr Val Val Glu Met Gln Thr Lys Gly Ser Glu Lys Trp Ser Thr Cys  
 18835 18840 18845  
 Thr Gln Val Lys Thr Leu Glu Ala Thr Ile Ser Gly Leu Thr Ala Gly  
 18850 18855 18860 1  
 Glu Glu Tyr Val Phe Arg Val Ala Ala Val Asn Glu Lys Gly Arg Ser  
 8865 18870 18875 18880  
 Asp Pro Arg Gln Leu Gly Val Pro Val Ile Ala Arg Asp Ile Glu Ile  
 18885 18890 18895  
 Lys Pro Ser Val Glu Leu Pro Phe His Thr Phe Asn Val Lys Ala Arg  
 18900 18905 18910  
 Glu Gln Leu Lys Ile Asp Val Pro Phe Lys Gly Arg Pro Gln Ala Thr  
 18915 18920 18925  
 Val Asn Trp Arg Lys Asp Gly Gln Thr Leu Lys Glu Thr Thr Arg Val  
 18930 18935 18940 1  
 Asn Val Ser Ser Ser Lys Thr Val Thr Ser Leu Ser Ile Lys Glu Ala  
 8945 18950 18955 18960  
 Ser Lys Glu Asp Val Gly Thr Tyr Glu Leu Cys Val Ser Asn Ser Ala  
 18965 18970 18975  
 Gly Ser Ile Thr Val Pro Ile Thr Ile Ile Val Leu Asp Arg Pro Gly  
 18980 18985 18990  
 Pro Pro Gly Pro Ile Arg Ile Asp Glu Val Ser Cys Asp Ser Ile Thr  
 18995 19000 19005  
 Ile Ser Trp Asn Pro Pro Glu Tyr Asp Gly Gly Cys Gln Ile Ser Asn  
 19010 19015 19020 1  
 Tyr Ile Val Glu Lys Lys Glu Thr Thr Ser Thr Thr Trp His Ile Val  
 9025 19030 19035 19040  
 Ser Gln Ala Val Ala Arg Thr Ser Ile Lys Ile Val Arg Leu Thr Thr  
 19045 19050 19055  
 Gly Ser Glu Tyr Gln Phe Arg Val Cys Ala Glu Asn Arg Tyr Gly Lys  
 19060 19065 19070

Ser Ser Tyr Ser Glu Ser Ser Ala Val Val Ala Glu Tyr Pro Phe Ser  
 19075 19080 19085  
 Pro Pro Gly Pro Pro Gly Thr Pro Lys Val Val His Ala Thr Lys Ser  
 19090 19095 19100 1  
 Thr Met Leu Val Thr Trp Gln Val Pro Val Asn Asp Gly Gly Ser Arg  
 9105 19110 19115 19120  
 Val Ile Gly Tyr His Leu Glu Tyr Lys Glu Arg Ser Ser Ile Leu Trp  
 19125 19130 19135  
 Ser Lys Ala Asn Lys Ile Leu Ile Ala Asp Thr Gln Val Lys Val Ser  
 19140 19145 19150  
 Gly Leu Asp Glu Gly Leu Met Tyr Glu Tyr Arg Val Tyr Ala Glu Asn  
 19155 19160 19165  
 Ile Ala Gly Ile Gly Lys Cys Ser Lys Ser Cys Glu Pro Val Pro Ala  
 19170 19175 19180 1  
 Arg Asp Pro Cys Asp Pro Pro Gly Gln Pro Glu Val Thr Asn Ile Thr  
 9185 19190 19195 19200  
 Arg Lys Ser Val Ser Leu Lys Trp Ser Lys Pro His Tyr Asp Gly Gly  
 19205 19210 19215  
 Ala Lys Ile Thr Gly Tyr Ile Val Glu Arg Arg Glu Leu Pro Asp Gly  
 19220 19225 19230  
 Arg Trp Leu Lys Cys Asn Tyr Thr Asn Ile Gln Glu Thr Tyr Phe Glu  
 19235 19240 19245  
 Val Thr Glu Leu Thr Glu Asp Gln Arg Tyr Glu Phe Arg Val Phe Ala  
 19250 19255 19260 1  
 Arg Asn Ala Ala Asp Ser Val Ser Glu Pro Ser Glu Ser Thr Gly Pro  
 9265 19270 19275 19280  
 Ile Ile Val Lys Asp Asp Val Glu Pro Pro Arg Val Met Met Asp Val  
 19285 19290 19295  
 Lys Phe Arg Asp Val Ile Val Val Lys Ala Gly Glu Val Leu Lys Ile  
 19300 19305 19310  
 Asn Ala Asp Ile Ala Gly Arg Pro Leu Pro Val Ile Ser Trp Ala Lys  
 19315 19320 19325  
 Asp Gly Ile Glu Ile Glu Glu Arg Ala Arg Thr Glu Ile Ile Ser Thr  
 19330 19335 19340 1  
 Asp Asn His Thr Leu Leu Thr Val Lys Asp Cys Ile Arg Arg Asp Thr  
 9345 19350 19355 19360  
 Gly Gln Tyr Val Leu Thr Leu Lys Asn Val Ala Gly Thr Arg Ser Val  
 19365 19370 19375  
 Ala Val Asn Cys Lys Val Leu Asp Lys Pro Gly Pro Pro Ala Gly Pro  
 19380 19385 19390  
 Leu Glu Ile Asn Gly Leu Thr Ala Glu Lys Cys Ser Leu Ser Trp Gly  
 19395 19400 19405  
 Arg Pro Gln Glu Asp Gly Gly Ala Asp Ile Asp Tyr Tyr His Arg Lys  
 19410 19415 19420 1  
 Lys Arg Glu Thr Ser His Leu Ala Trp Thr Ile Cys Glu Gly Glu Leu  
 9425 19430 19435 19440  
 Gln Met Thr Ser Cys Lys Val Thr Lys Leu Leu Lys Gly Asn Glu Tyr  
 19445 19450 19455  
 Ile Phe Arg Val Thr Gly Val Asn Lys Tyr Gly Val Gly Glu Pro Leu  
 19460 19465 19470  
 Glu Ser Val Ala Ile Lys Ala Leu Asp Pro Phe Thr Val Pro Ser Pro  
 19475 19480 19485  
 Pro Thr Ser Leu Glu Ile Thr Ser Val Thr Lys Glu Ser Met Thr Leu  
 19490 19495 19500 1  
 Cys Trp Ser Arg Pro Glu Ser Asp Gly Gly Ser Glu Ile Ser Gly Tyr  
 9505 19510 19515 19520  
 Ile Ile Glu Arg Arg Glu Lys Asn Ser Leu Arg Trp Val Arg Val Asn  
 19525 19530 19535  
 Lys Lys Pro Val Tyr Asp Leu Arg Val Lys Ser Thr Gly Leu Arg Glu  
 19540 19545 19550  
 Gly Cys Glu Tyr Glu Tyr Arg Val Tyr Ala Glu Asn Ala Ala Gly Leu  
 19555 19560 19565



Ser Leu Pro Ser Glu Thr Ser Pro Leu Ile Arg Ala Glu Asp Pro Val  
 19570 19575 19580 1  
 Phe Leu Pro Ser Pro Pro Ser Lys Pro Lys Ile Val Asp Ser Gly Lys  
 9585 19590 19595 19600  
 Thr Thr Ile Thr Ile Ala Trp Val Lys Pro Leu Phe Asp Gly Gly Ala  
 19605 19610 19615  
 Pro Ile Thr Gly Tyr Thr Val Glu Tyr Lys Lys Ser Asp Asp Thr Asp  
 19620 19625 19630  
 Trp Lys Thr Ser Ile Gln Ser Leu Arg Gly Thr Glu Tyr Thr Ile Ser  
 19635 19640 19645  
 Gly Leu Thr Thr Gly Ala Glu Tyr Val Phe Arg Val Lys Ser Val Asn  
 19650 19655 19660 1  
 Lys Val Gly Ala Ser Asp Pro Ser Asp Ser Ser Asp Pro Gln Ile Ala  
 9665 19670 19675 19680  
 Lys Glu Arg Glu Glu Pro Leu Phe Asp Ile Asp Ser Glu Met Arg  
 19685 19690 19695  
 Lys Thr Leu Ile Val Lys Ala Gly Ala Ser Phe Thr Met Thr Val Pro  
 19700 19705 19710  
 Phe Arg Gly Arg Pro Val Pro Asn Val Leu Trp Ser Lys Pro Asp Thr  
 19715 19720 19725  
 Asp Leu Arg Thr Arg Ala Tyr Val Asp Thr Thr Asp Ser Arg Thr Ser  
 19730 19735 19740 1  
 Leu Thr Ile Glu Asn Ala Asn Arg Asn Asp Ser Gly Lys Tyr Thr Leu  
 9745 19750 19755 19760  
 Thr Ile Gln Asn Val Leu Ser Ala Ala Ser Leu Thr Leu Val Val Lys  
 19765 19770 19775  
 Val Leu Asp Thr Pro Gly Pro Pro Thr Asn Ile Thr Val Gln Asp Val  
 19780 19785 19790  
 Thr Lys Glu Ser Ala Val Leu Ser Trp Asp Val Pro Glu Asn Asp Gly  
 19795 19800 19805  
 Gly Ala Pro Val Lys Asn Tyr His Ile Glu Lys Arg Glu Ala Ser Lys  
 19810 19815 19820 1  
 Lys Ala Trp Val Ser Val Thr Asn Asn Cys Asn Arg Leu Ser Tyr Lys  
 9825 19830 19835 19840  
 Val Thr Asn Leu Gln Glu Gly Ala Ile Tyr Tyr Phe Arg Val Ser Gly  
 19845 19850 19855  
 Glu Asn Glu Phe Gly Val Gly Ile Pro Ala Glu Thr Lys Glu Gly Val  
 19860 19865 19870  
 Lys Ile Thr Glu Lys Pro Ser Pro Pro Glu Lys Leu Gly Val Thr Ser  
 19875 19880 19885  
 Ile Ser Lys Asp Ser Val Ser Leu Thr Trp Leu Lys Pro Glu His Asp  
 19890 19895 19900 1  
 Gly Gly Ser Arg Ile Val His Tyr Val Val Glu Ala Leu Glu Lys Gly  
 9905 19910 19915 19920  
 Gln Lys Asn Trp Val Lys Cys Ala Val Ala Lys Ser Thr His His Val  
 19925 19930 19935  
 Val Ser Gly Leu Arg Glu Asn Ser Glu Tyr Phe Phe Arg Val Phe Ala  
 19940 19945 19950  
 Glu Asn Gln Ala Gly Leu Ser Asp Pro Arg Glu Leu Leu Pro Val  
 19955 19960 19965  
 Leu Ile Lys Glu Gln Leu Glu Pro Pro Glu Ile Asp Met Lys Asn Phe  
 19970 19975 19980 1  
 Pro Ser His Thr Val Tyr Val Arg Ala Gly Ser Asn Leu Lys Val Asp  
 9985 19990 19995 20000  
 Ile Pro Ile Ser Gly Lys Pro Leu Pro Lys Val Thr Leu Ser Arg Asp  
 20005 20010 20015  
 Gly Val Pro Leu Lys Ala Thr Met Arg Phe Asn Thr Glu Ile Thr Ala  
 20020 20025 20030  
 Glu Asn Leu Thr Ile Asn Leu Lys Glu Ser Val Thr Ala Asp Ala Gly  
 20035 20040 20045  
 Arg Tyr Glu Ile Thr Ala Ala Asn Ser Ser Gly Thr Thr Lys Ala Phe  
 20050 20055 20060 2

Ile Asn Ile Val Val Leu Asp Arg Pro Gly Pro Pro Thr Gly Pro Val  
 0065 20070 20075 20080  
 Val Ile Ser Asp Ile Thr Glu Glu Ser Val Thr Leu Lys Trp Glu Pro  
 20085 20090 20095  
 Pro Lys Tyr Asp Gly Gly Ser Gln Val Thr Asn Tyr Ile Leu Leu Lys  
 20100 20105 20110  
 Arg Glu Thr Ser Thr Ala Val Trp Thr Glu Val Ser Ala Thr Val Ala  
 20115 20120 20125  
 Arg Thr Met Met Lys Val Met Lys Leu Thr Thr Gly Glu Glu Tyr Gln  
 20130 20135 20140 2  
 Phe Arg Ile Lys Ala Glu Asn Arg Phe Gly Ile Ser Asp His Ile Asp  
 0145 20150 20155 20160  
 Ser Ala Cys Val Thr Val Lys Leu Pro Tyr Thr Thr Pro Gly Pro Pro  
 20165 20170 20175  
 Ser Thr Pro Trp Val Thr Asn Val Thr Arg Glu Ser Ile Thr Val Gly  
 20180 20185 20190  
 Trp His Glu Pro Val Ser Asn Gly Gly Ser Ala Val Val Gly Tyr His  
 20195 20200 20205  
 Leu Glu Met Lys Asp Arg Asn Ser Ile Leu Trp Gln Lys Ala Asn Lys  
 20210 20215 20220 2  
 Leu Val Ile Arg Thr Thr His Phe Lys Val Thr Thr Ile Ser Ala Gly  
 0225 20230 20235 20240  
 Leu Ile Tyr Glu Phe Arg Val Tyr Ala Glu Asn Ala Ala Gly Val Gly  
 20245 20250 20255  
 Lys Pro Ser His Pro Ser Glu Pro Val Leu Ala Ile Asp Ala Cys Glu  
 20260 20265 20270  
 Pro Pro Arg Asn Val Arg Ile Thr Asp Ile Ser Lys Asn Ser Val Ser  
 20275 20280 20285  
 Leu Ser Trp Gln Gln Pro Ala Phe Asp Gly Gly Ser Lys Ile Thr Gly  
 20290 20295 20300 2  
 Tyr Ile Val Glu Arg Arg Asp Leu Pro Asp Gly Arg Trp Thr Lys Ala  
 0305 20310 20315 20320  
 Ser Phe Thr Asn Val Thr Glu Thr Gln Phe Thr Ile Ser Gly Leu Thr  
 20325 20330 20335  
 Gln Asn Ser Gln Tyr Glu Phe Arg Val Phe Ala Arg Asn Ala Val Gly  
 20340 20345 20350  
 Ser Ile Ser Asn Pro Ser Glu Val Val Gly Pro Ile Thr Cys Ile Asp  
 20355 20360 20365  
 Ser Tyr Gly Gly Pro Val Ile Asp Leu Pro Leu Glu Tyr Thr Glu Val  
 20370 20375 20380 2  
 Val Lys Tyr Arg Ala Gly Thr Ser Val Lys Leu Arg Ala Gly Ile Ser  
 0385 20390 20395 20400  
 Gly Lys Pro Ala Pro Thr Ile Glu Trp Tyr Lys Asp Asp Lys Glu Leu  
 20405 20410 20415  
 Gln Thr Asn Ala Leu Val Cys Val Glu Asn Thr Thr Asp Leu Ala Ser  
 20420 20425 20430  
 Ile Leu Ile Lys Asp Ala Asp Arg Leu Asn Ser Gly Cys Tyr Glu Leu  
 20435 20440 20445  
 Lys Leu Arg Asn Ala Met Ala Ser Ala Ser Ala Thr Ile Arg Val Gln  
 20450 20455 20460 2  
 Ile Leu Asp Lys Pro Gly Pro Pro Gly Gly Pro Ile Glu Phe Lys Thr  
 0465 20470 20475 20480  
 Val Thr Ala Glu Lys Ile Thr Leu Leu Trp Arg Pro Pro Ala Asp Asp  
 20485 20490 20495  
 Gly Gly Ala Lys Ile Thr His Tyr Ile Val Glu Lys Arg Glu Thr Ser  
 20500 20505 20510  
 Arg Val Val Trp Ser Met Val Ser Glu His Leu Glu Glu Cys Ile Ile  
 20515 20520 20525  
 Thr Thr Thr Lys Ile Ile Lys Gly Asn Glu Tyr Ile Phe Arg Val Arg  
 20530 20535 20540 2  
 Ala Val Asn Lys Tyr Gly Ile Gly Glu Pro Leu Glu Ser Asp Ser Val  
 0545 20550 20555 20560

Val Ala Lys Asn Ala Phe Val Thr Pro Gly Pro Pro Gly Ile Pro Glu  
 20565 20570 20575  
 Val Thr Lys Ile Thr Lys Asn Ser Met Thr Val Val Trp Ser Arg Pro  
 20580 20585 20590  
 Ile Ala Asp Gly Gly Ser Asp Ile Ser Gly Tyr Phe Leu Glu Lys Arg  
 20595 20600 20605  
 Asp Lys Lys Ser Leu Gly Trp Phe Lys Val Leu Lys Glu Thr Ile Arg  
 20610 20615 20620 2  
 Asp Thr Arg Gln Lys Val Thr Gly Leu Thr Glu Asn Ser Asp Tyr Gln  
 0625 20630 20635 20640  
 Tyr Arg Val Cys Ala Val Asn Ala Ala Gly Gln Gly Pro Phe Ser Glu  
 20645 20650 20655  
 Pro Ser Glu Phe Tyr Lys Ala Ala Asp Pro Ile Asp Pro Pro Gly Pro  
 20660 20665 20670  
 Pro Ala Lys Ile Arg Ile Ala Asp Ser Thr Lys Ser Ser Ile Thr Leu  
 20675 20680 20685  
 Gly Trp Ser Lys Pro Val Tyr Asp Gly Gly Ser Ala Val Thr Gly Tyr  
 20690 20695 20700 2  
 Val Val Glu Ile Arg Gln Gly Glu Glu Glu Glu Trp Thr Thr Val Ser  
 0705 20710 20715 20720  
 Thr Lys Gly Glu Val Arg Thr Thr Glu Tyr Val Val Ser Asn Leu Lys  
 20725 20730 20735  
 Pro Gly Val Asn Tyr Tyr Phe Arg Val Ser Ala Val Asn Cys Ala Gly  
 20740 20745 20750  
 Gln Gly Glu Pro Ile Glu Met Asn Glu Pro Val Gln Ala Lys Asp Ile  
 20755 20760 20765  
 Leu Glu Ala Pro Glu Ile Asp Leu Asp Val Ala Leu Arg Thr Ser Val  
 20770 20775 20780 2  
 Ile Ala Lys Ala Gly Glu Asp Val Gln Val Leu Ile Pro Phe Lys Gly  
 0785 20790 20795 20800  
 Arg Pro Pro Pro Thr Val Thr Trp Arg Lys Asp Glu Lys Asn Leu Gly  
 20805 20810 20815  
 Ser Asp Ala Arg Tyr Ser Ile Glu Asn Thr Asp Ser Ser Ser Leu Leu  
 20820 20825 20830  
 Thr Ile Pro Gln Val Thr Arg Asn Asp Thr Gly Lys Tyr Ile Leu Thr  
 20835 20840 20845  
 Ile Glu Asn Gly Val Gly Glu Pro Lys Ser Ser Thr Val Ser Val Lys  
 20850 20855 20860 2  
 Val Leu Asp Thr Pro Ala Ala Cys Gln Lys Leu Gln Val Lys His Val  
 0865 20870 20875 20880  
 Ser Arg Gly Thr Val Thr Leu Leu Trp Asp Pro Pro Leu Ile Asp Gly  
 20885 20890 20895  
 Gly Ser Pro Ile Ile Asn Tyr Val Ile Glu Lys Arg Asp Ala Thr Lys  
 20900 20905 20910  
 Arg Thr Trp Ser Val Val Ser His Lys Cys Ser Ser Thr Ser Phe Lys  
 20915 20920 20925  
 Leu Ile Asp Leu Ser Glu Lys Thr Pro Phe Phe Phe Arg Val Leu Ala  
 20930 20935 20940 2  
 Glu Asn Glu Ile Gly Ile Gly Glu Pro Cys Glu Thr Thr Glu Pro Val  
 0945 20950 20955 20960  
 Lys Ala Ala Glu Val Pro Ala Pro Ile Arg Asp Leu Ser Met Lys Asp  
 20965 20970 20975  
 Ser Thr Lys Thr Ser Val Ile Leu Ser Trp Thr Lys Pro Asp Phe Asp  
 20980 20985 20990  
 Gly Gly Ser Val Ile Thr Glu Tyr Val Val Glu Arg Lys Gly Lys Gly  
 20995 21000 21005  
 Glu Gln Thr Trp Ser His Ala Gly Ile Ser Lys Thr Cys Glu Ile Glu  
 21010 21015 21020 2  
 Val Ser Gln Leu Lys Glu Gln Ser Val Leu Glu Phe Arg Val Phe Ala  
 1025 21030 21035 21040  
 Lys Asn Glu Lys Gly Leu Ser Asp Pro Val Thr Ile Gly Pro Ile Thr  
 21045 21050 21055

Val Lys Glu Leu Ile Ile Thr Pro Glu Val Asp Leu Ser Asp Ile Pro  
 21060 21065 21070  
 Gly Ala Gln Val Thr Val Arg Ile Gly His Asn Val His Leu Glu Leu  
 21075 21080 21085  
 Pro Tyr Lys Gly Lys Pro Lys Pro Ser Ile Ser Trp Leu Lys Asp Gly  
 21090 21095 21100 2  
 Leu Pro Leu Lys Glu Ser Glu Phe Val Arg Phe Ser Lys Thr Glu Asn  
 1105 21110 21115 21120  
 Lys Ile Thr Leu Ser Ile Lys Asn Ala Lys Lys Glu His Gly Gly Lys  
 21125 21130 21135  
 Tyr Thr Val Ile Leu Asp Asn Ala Val Cys Arg Ile Ala Val Pro Ile  
 21140 21145 21150  
 Thr Val Ile Thr Leu Gly Pro Pro Ser Lys Pro Lys Gly Pro Ile Arg  
 21155 21160 21165  
 Phe Asp Glu Ile Lys Ala Asp Ser Val Ile Leu Ser Trp Asp Val Pro  
 21170 21175 21180 2  
 Glu Asp Asn Gly Gly Gly Glu Ile Thr Cys Tyr Ser Ile Glu Lys Arg  
 1185 21190 21195 21200  
 Glu Thr Ser Gln Thr Asn Trp Lys Met Val Cys Ser Ser Val Ala Arg  
 21205 21210 21215  
 Thr Thr Phe Lys Val Pro Asn Leu Val Lys Asp Ala Glu Tyr Gln Phe  
 21220 21225 21230  
 Arg Val Arg Ala Glu Asn Arg Tyr Gly Val Ser Gln Pro Leu Val Ser  
 21235 21240 21245  
 Ser Ile Ile Val Ala Lys His Gln Phe Arg Ile Pro Gly Pro Pro Gly  
 21250 21255 21260 2  
 Lys Pro Val Ile Tyr Asn Val Thr Ser Asp Gly Met Ser Leu Thr Trp  
 1265 21270 21275 21280  
 Asp Ala Pro Val Tyr Asp Gly Gly Ser Glu Val Thr Gly Phe His Val  
 21285 21290 21295  
 Glu Lys Lys Glu Arg Asn Ser Ile Leu Trp Gln Lys Val Asn Thr Ser  
 21300 21305 21310  
 Pro Ile Ser Gly Arg Glu Tyr Arg Ala Thr Gly Leu Val Glu Gly Leu  
 21315 21320 21325  
 Asp Tyr Gln Phe Arg Val Tyr Ala Glu Asn Ser Ala Gly Leu Ser Ser  
 21330 21335 21340 2  
 Pro Ser Asp Pro Ser Lys Phe Thr Leu Ala Val Ser Pro Val Asp Pro  
 1345 21350 21355 21360  
 Pro Gly Thr Pro Asp Tyr Ile Asp Val Thr Arg Glu Thr Ile Thr Leu  
 21365 21370 21375  
 Lys Trp Asn Pro Pro Leu Arg Asp Gly Gly Ser Lys Ile Val Gly Tyr  
 21380 21385 21390  
 Ser Ile Glu Lys Arg Gln Gly Asn Glu Arg Trp Val Arg Cys Asn Phe  
 21395 21400 21405  
 Thr Asp Val Ser Glu Cys Gln Tyr Thr Val Thr Gly Leu Ser Pro Gly  
 21410 21415 21420 2  
 Asp Arg Tyr Glu Phe Arg Ile Ile Ala Arg Asn Ala Val Gly Thr Ile  
 1425 21430 21435 21440  
 Ser Pro Pro Ser Gln Ser Ser Gly Ile Ile Met Thr Arg Asp Glu Asn  
 21445 21450 21455  
 Val Pro Pro Ile Val Glu Phe Gly Pro Glu Tyr Phe Asp Gly Leu Ile  
 21460 21465 21470  
 Ile Lys Ser Gly Glu Ser Leu Arg Ile Lys Ala Leu Val Gln Gly Arg  
 21475 21480 21485  
 Pro Val Pro Arg Val Thr Trp Phe Lys Asp Gly Val Glu Ile Glu Lys  
 21490 21495 21500 2  
 Arg Met Asn Met Glu Ile Thr Asn Val Leu Gly Ser Thr Ser Leu Phe  
 1505 21510 21515 21520  
 Val Arg Asp Ala Thr Arg Asp His Arg Gly Val Tyr Thr Val Glu Ala  
 21525 21530 21535  
 Lys Asn Ala Ser Gly Ser Ala Lys Ala Glu Ile Lys Val Lys Val Gln  
 21540 21545 21550

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Asp Thr Pro Gly Lys Val Val Gly Pro Ile Arg Phe Thr Asn Ile Thr
  21555                21560                21565
Gly Glu Lys Met Thr Leu Trp Trp Asp Ala Pro Leu Asn Asp Gly Cys
  21570                21575                21580                2
Ala Pro Ile Thr His Tyr Ile Ile Glu Lys Arg Glu Thr Ser Arg Leu
1585                21590                21595                21600
Ala Trp Ala Leu Ile Glu Asp Lys Cys Glu Ala Gln Ser Tyr Thr Ala
                21605                21610                21615
Ile Lys Leu Ile Asn Gly Asn Glu Tyr Gln Phe Arg Val Ser Ala Val
                21620                21625                21630
Asn Lys Phe Gly Val Gly Arg Pro Leu Asp Ser Asp Pro Val Val Ala
                21635                21640                21645
Gln Ile Gln Tyr Thr Val Pro Asp Ala Pro Gly Ile Pro Glu Pro Ser
                21650                21655                21660                2
Asn Ile Thr Gly Asn Ser Ile Thr Leu Thr Trp Ala Arg Pro Glu Ser
1665                21670                21675                21680
Asp Gly Gly Ser Glu Ile Gln Gln Tyr Ile Leu Glu Arg Arg Glu Lys
                21685                21690                21695
Lys Ser Thr Arg Trp Val Lys Val Ile Ser Lys Arg Pro Ile Ser Glu
                21700                21705                21710
Thr Arg Phe Lys Val Thr Gly Leu Thr Glu Gly Asn Glu Tyr Glu Phe
                21715                21720                21725
His Val Met Ala Glu Asn Ala Ala Gly Val Gly Pro Ala Ser Gly Ile
                21730                21735                21740                2
Ser Arg Leu Ile Lys Cys Arg Glu Pro Val Asn Pro Pro Gly Pro Pro
1745                21750                21755                21760
Thr Val Val Lys Val Thr Asp Thr Ser Lys Thr Thr Val Ser Leu Glu
                21765                21770                21775
Trp Ser Lys Pro Val Phe Asp Gly Gly Met Glu Ile Ile Gly Tyr Ile
                21780                21785                21790
Ile Glu Met Cys Lys Thr Asp Leu Gly Asp Trp His Lys Val Asn Ala
                21795                21800                21805
Glu Ala Cys Val Lys Thr Arg Tyr Thr Val Thr Asp Leu Gln Ala Gly
                21810                21815                21820                2
Glu Glu Tyr Lys Phe Arg Val Ser Ala Ile Asn Gly Ala Gly Lys Gly
1825                21830                21835                21840
Asp Ser Cys Glu Val Thr Gly Thr Ile Lys Ala Val Asp Arg Leu Thr
                21845                21850                21855
Ala Pro Glu Leu Asp Ile Asp Ala Asn Phe Lys Gln Thr His Val Val
                21860                21865                21870
Arg Ala Gly Ala Ser Ile Arg Leu Phe Ile Ala Tyr Gln Gly Arg Pro
                21875                21880                21885
Thr Pro Thr Ala Val Trp Ser Lys Pro Asp Ser Asn Leu Ser Leu Arg
                21890                21895                21900                2
Ala Asp Ile His Thr Thr Asp Ser Phe Ser Thr Leu Thr Val Glu Asn
1905                21910                21915                21920
Cys Asn Arg Asn Asp Ala Gly Lys Tyr Thr Leu Thr Val Glu Asn Asn
                21925                21930                21935
Ser Gly Ser Lys Ser Ile Thr Phe Thr Val Lys Val Leu Asp Thr Pro
                21940                21945                21950
Gly Pro Pro Gly Pro Ile Thr Phe Lys Asp Val Thr Arg Gly Ser Ala
                21955                21960                21965
Thr Leu Met Trp Asp Ala Pro Leu Leu Asp Gly Gly Ala Arg Ile His
                21970                21975                21980                2
His Tyr Val Val Glu Lys Arg Glu Ala Ser Arg Arg Ser Trp Gln Val
1985                21990                21995                22000
Ile Ser Glu Lys Cys Thr Arg Gln Ile Phe Lys Val Asn Asp Leu Ala
                22005                22010                22015
Glu Gly Val Pro Tyr Tyr Phe Arg Val Ser Ala Val Asn Glu Tyr Gly
                22020                22025                22030
Val Gly Glu Pro Tyr Glu Met Pro Glu Pro Ile Val Ala Thr Glu Gln
                22035                22040                22045

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Pro Ala Pro Pro Arg Arg Leu Asp Val Val Asp Thr Ser Lys Ser Ser  
 22050 22055 22060 2  
 Ala Val Leu Ala Trp Leu Lys Pro Asp His Asp Gly Gly Ser Arg Ile  
 2065 22070 22075 22080  
 Thr Gly Tyr Leu Leu Glu Met Arg Gln Lys Gly Ser Asp Leu Trp Val  
 22085 22090 22095  
 Glu Ala Gly His Thr Lys Gln Leu Thr Phe Thr Val Glu Arg Leu Val  
 22100 22105 22110  
 Glu Lys Thr Glu Tyr Glu Phe Arg Val Lys Ala Lys Asn Asp Ala Gly  
 22115 22120 22125  
 Tyr Ser Glu Pro Arg Glu Ala Phe Ser Ser Val Ile Ile Lys Glu Pro  
 22130 22135 22140 2  
 Gln Ile Glu Pro Thr Ala Asp Leu Thr Gly Ile Thr Asn Gln Leu Ile  
 2145 22150 22155 22160  
 Thr Cys Lys Ala Gly Ser Pro Phe Thr Ile Asp Val Pro Ile Ser Gly  
 22165 22170 22175  
 Arg Pro Ala Pro Lys Val Thr Trp Lys Leu Glu Glu Met Arg Leu Lys  
 22180 22185 22190  
 Glu Thr Asp Arg Val Ser Ile Thr Thr Thr Lys Asp Arg Thr Thr Leu  
 22195 22200 22205  
 Thr Val Lys Asp Ser Met Arg Gly Asp Ser Gly Arg Tyr Phe Leu Thr  
 22210 22215 22220 2  
 Leu Glu Asn Thr Ala Gly Val Lys Thr Phe Ser Val Thr Val Val Val  
 2225 22230 22235 22240  
 Ile Gly Arg Pro Gly Pro Val Thr Gly Pro Ile Glu Val Ser Ser Val  
 22245 22250 22255  
 Ser Ala Glu Ser Cys Val Leu Ser Trp Gly Glu Pro Lys Asp Gly Gly  
 22260 22265 22270  
 Gly Thr Glu Ile Thr Asn Tyr Ile Val Glu Lys Arg Glu Ser Gly Thr  
 22275 22280 22285  
 Thr Ala Trp Gln Leu Val Asn Ser Ser Val Lys Arg Thr Gln Ile Lys  
 22290 22295 22300 2  
 Val Thr His Leu Thr Lys Tyr Met Glu Tyr Ser Phe Arg Val Ser Ser  
 2305 22310 22315 22320  
 Glu Asn Arg Phe Gly Val Ser Lys Pro Leu Glu Ser Ala Pro Ile Ile  
 22325 22330 22335  
 Ala Glu His Pro Phe Val Pro Pro Ser Ala Pro Thr Arg Pro Glu Val  
 22340 22345 22350  
 Tyr His Val Ser Ala Asn Ala Met Ser Ile Arg Trp Glu Glu Pro Tyr  
 22355 22360 22365  
 His Asp Gly Gly Ser Lys Ile Ile Gly Tyr Trp Val Glu Lys Lys Glu  
 22370 22375 22380 2  
 Arg Asn Thr Ile Leu Trp Val Lys Glu Asn Lys Val Pro Cys Leu Glu  
 2385 22390 22395 22400  
 Cys Asn Tyr Lys Val Thr Gly Leu Val Glu Gly Leu Glu Tyr Gln Phe  
 22405 22410 22415  
 Arg Thr Tyr Ala Leu Asn Ala Ala Gly Val Ser Lys Ala Ser Glu Ala  
 22420 22425 22430  
 Ser Arg Pro Ile Met Ala Gln Asn Pro Val Asp Ala Pro Gly Arg Pro  
 22435 22440 22445  
 Glu Val Thr Asp Val Thr Arg Ser Thr Val Ser Leu Ile Trp Ser Ala  
 22450 22455 22460 2  
 Pro Ala Tyr Asp Gly Gly Ser Lys Val Val Gly Tyr Ile Ile Glu Arg  
 2465 22470 22475 22480  
 Lys Pro Val Ser Glu Val Gly Asp Gly Arg Trp Leu Lys Cys Asn Tyr  
 22485 22490 22495  
 Thr Ile Val Ser Asp Asn Phe Phe Thr Val Thr Ala Leu Ser Glu Gly  
 22500 22505 22510  
 Asp Thr Tyr Glu Phe Arg Val Leu Ala Lys Asn Ala Ala Gly Val Ile  
 22515 22520 22525  
 Ser Lys Gly Ser Glu Ser Thr Gly Pro Val Thr Cys Arg Asp Glu Tyr  
 22530 22535 22540 2

Ala Pro Pro Lys Ala Glu Leu Asp Ala Arg Leu His Gly Asp Leu Val  
 2545 22550 22555 22560  
 Thr Ile Arg Ala Gly Ser Asp Leu Val Leu Asp Ala Ala Val Gly Gly  
 22565 22570 22575  
 Lys Pro Glu Pro Lys Ile Ile Trp Thr Lys Gly Asp Lys Glu Leu Asp  
 22580 22585 22590  
 Leu Cys Glu Lys Val Ser Leu Gln Tyr Thr Gly Lys Arg Ala Thr Ala  
 22595 22600 22605  
 Val Ile Lys Phe Cys Asp Arg Ser Asp Ser Gly Lys Tyr Thr Leu Thr  
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 Val Lys Asn Ala Ser Gly Thr Lys Ala Val Ser Val Met Val Lys Val  
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 Leu Asp Ser Pro Gly Pro Cys Gly Lys Leu Thr Val Ser Arg Val Thr  
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 Gln Glu Lys Cys Thr Leu Ala Trp Ser Leu Pro Gln Glu Asp Gly Gly  
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 Ala Glu Ile Thr His Tyr Ile Val Glu Arg Arg Glu Thr Ser Arg Leu  
 22675 22680 22685  
 Asn Trp Val Ile Val Glu Gly Glu Cys Pro Thr Leu Ser Tyr Val Val  
 22690 22695 22700 2  
 Thr Arg Leu Ile Lys Asn Asn Glu Tyr Ile Phe Arg Val Arg Ala Val  
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 Asn Lys Tyr Gly Pro Gly Val Pro Val Glu Ser Glu Pro Ile Val Ala  
 22725 22730 22735  
 Arg Asn Ser Phe Thr Ile Pro Ser Pro Pro Gly Ile Pro Glu Glu Val  
 22740 22745 22750  
 Gly Thr Gly Lys Glu His Ile Ile Ile Gln Trp Thr Lys Pro Glu Ser  
 22755 22760 22765  
 Asp Gly Gly Asn Glu Ile Ser Asn Tyr Leu Val Asp Lys Arg Glu Lys  
 22770 22775 22780 2  
 Glu Ser Leu Arg Trp Thr Arg Val Asn Lys Asp Tyr Val Val Tyr Asp  
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 Thr Arg Leu Lys Val Thr Ser Leu Met Glu Gly Cys Asp Tyr Gln Phe  
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 Ser Asn Phe Ile Ser Cys Arg Glu Pro Ser Tyr Thr Pro Gly Pro Pro  
 22835 22840 22845  
 Ser Ala Pro Arg Val Val Asp Thr Thr Lys His Ser Ile Ser Leu Ala  
 22850 22855 22860 2  
 Trp Thr Lys Pro Met Tyr Asp Gly Gly Thr Asp Ile Val Gly Tyr Val  
 2865 22870 22875 22880  
 Leu Glu Met Gln Glu Lys Asp Thr Asp Gln Trp Tyr Arg Val His Thr  
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 Asn Ala Thr Ile Arg Asn Thr Glu Phe Thr Val Pro Asp Leu Lys Met  
 22900 22905 22910  
 Gly Gln Lys Tyr Ser Phe Arg Val Ala Ala Val Asn Val Lys Gly Met  
 22915 22920 22925  
 Ser Glu Tyr Ser Glu Ser Ile Ala Glu Ile Glu Pro Val Glu Arg Ile  
 22930 22935 22940 2  
 Glu Ile Pro Asp Leu Glu Leu Ala Asp Asp Leu Lys Lys Thr Val Thr  
 2945 22950 22955 22960  
 Ile Arg Ala Gly Ala Ser Leu Arg Leu Met Val Ser Val Ser Gly Arg  
 22965 22970 22975  
 Pro Pro Pro Val Ile Thr Trp Ser Lys Gln Gly Ile Asp Leu Ala Ser  
 22980 22985 22990  
 Arg Ala Ile Ile Asp Thr Thr Glu Ser Tyr Ser Leu Leu Ile Val Asp  
 22995 23000 23005  
 Lys Val Asn Arg Tyr Asp Ala Gly Lys Tyr Thr Ile Glu Ala Glu Asn  
 23010 23015 23020 2  
 Gln Ser Gly Lys Lys Ser Ala Thr Val Leu Val Lys Val Tyr Asp Thr  
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Pro Gly Pro Cys Pro Ser Val Lys Val Lys Glu Val Ser Arg Asp Ser  
 23045 23050 23055  
 Val Thr Ile Thr Trp Glu Ile Pro Thr Ile Asp Gly Gly Ala Pro Ile  
 23060 23065 23070  
 Asn Asn Tyr Ile Val Glu Lys Arg Glu Ala Ala Met Arg Ala Phe Lys  
 23075 23080 23085  
 Thr Val Thr Thr Lys Cys Ser Lys Thr Leu Tyr Arg Ile Ser Gly Leu  
 23090 23095 23100 2  
 Val Glu Gly Thr Met His Tyr Phe Arg Val Leu Pro Glu Asn Ile Tyr  
 3105 23110 23115 23120  
 Gly Ile Gly Glu Pro Cys Glu Thr Ser Asp Ala Val Leu Val Ser Glu  
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 Val Pro Leu Val Pro Ala Lys Leu Glu Val Val Asp Val Thr Lys Ser  
 23140 23145 23150  
 Thr Val Thr Leu Ala Trp Glu Lys Pro Leu Tyr Asp Gly Gly Ser Arg  
 23155 23160 23165  
 Leu Thr Gly Tyr Val Leu Glu Ala Cys Lys Ala Gly Thr Glu Arg Trp  
 23170 23175 23180 2  
 Met Lys Val Val Thr Leu Lys Pro Thr Val Leu Glu His Thr Val Thr  
 3185 23190 23195 23200  
 Ser Leu Asn Glu Gly Glu Gln Tyr Leu Phe Arg Ile Arg Ala Gln Asn  
 23205 23210 23215  
 Glu Lys Gly Val Ser Glu Pro Arg Glu Thr Val Thr Ala Val Thr Val  
 23220 23225 23230  
 Gln Asp Leu Arg Val Leu Pro Thr Ile Asp Leu Ser Thr Met Pro Gln  
 23235 23240 23245  
 Lys Thr Ile His Val Pro Ala Gly Arg Pro Val Glu Leu Val Ile Pro  
 23250 23255 23260 2  
 Ile Ala Gly Arg Pro Pro Ala Ala Ser Trp Phe Phe Ala Gly Ser  
 3265 23270 23275 23280  
 Lys Leu Arg Glu Ser Glu Arg Val Thr Val Glu Thr His Thr Lys Val  
 23285 23290 23295  
 Ala Lys Leu Thr Ile Arg Glu Thr Thr Ile Arg Asp Thr Gly Glu Tyr  
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 Thr Leu Glu Leu Lys Asn Val Thr Gly Thr Thr Ser Glu Thr Ile Lys  
 23315 23320 23325  
 Val Ile Ile Leu Asp Lys Pro Gly Pro Pro Thr Gly Pro Ile Lys Ile  
 23330 23335 23340 2  
 Asp Glu Ile Asp Ala Thr Ser Ile Thr Ile Ser Trp Glu Pro Pro Glu  
 3345 23350 23355 23360  
 Leu Asp Gly Gly Ala Pro Leu Ser Gly Tyr Val Val Glu Gln Arg Asp  
 23365 23370 23375  
 Ala His Arg Pro Gly Trp Leu Pro Val Ser Glu Ser Val Thr Arg Ser  
 23380 23385 23390  
 Thr Phe Lys Phe Thr Arg Leu Thr Glu Gly Asn Glu Tyr Val Phe Arg  
 23395 23400 23405  
 Val Ala Ala Thr Asn Arg Phe Gly Ile Gly Ser Tyr Leu Gln Ser Glu  
 23410 23415 23420 2  
 Val Ile Glu Cys Arg Ser Ile Arg Ile Pro Gly Pro Pro Glu Thr  
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 Leu Gln Ile Phe Asp Val Ser Arg Asp Gly Met Thr Leu Thr Trp Tyr  
 23445 23450 23455  
 Pro Pro Glu Asp Asp Gly Gly Ser Gln Val Thr Gly Tyr Ile Val Glu  
 23460 23465 23470  
 Arg Lys Glu Val Arg Ala Asp Arg Trp Val Arg Val Asn Lys Val Pro  
 23475 23480 23485  
 Val Thr Met Thr Arg Tyr Arg Ser Thr Gly Leu Thr Glu Gly Leu Glu  
 23490 23495 23500 2  
 Tyr Glu His Arg Val Thr Ala Ile Asn Ala Arg Gly Ser Gly Lys Pro  
 3505 23510 23515 23520  
 Ser Arg Pro Ser Lys Pro Ile Val Ala Met Asp Pro Ile Ala Pro Pro  
 23525 23530 23535



Gly Lys Pro Gln Asn Pro Arg Val Thr Asp Thr Thr Arg Thr Ser Val  
 23540 23545 23550  
 Ser Leu Ala Trp Ser Val Pro Glu Asp Glu Gly Gly Ser Lys Val Thr  
 23555 23560 23565  
 Gly Tyr Leu Ile Glu Met Gln Lys Val Asp Gln His Glu Trp Thr Lys  
 23570 23575 23580 2  
 Cys Asn Thr Thr Pro Thr Lys Ile Arg Glu Tyr Thr Leu Thr His Leu  
 3585 23590 23595 23600  
 Pro Gln Gly Ala Glu Tyr Arg Phe Arg Val Leu Ala Cys Asn Ala Gly  
 23605 23610 23615  
 Gly Pro Gly Glu Pro Ala Glu Val Pro Gly Thr Val Lys Val Thr Glu  
 23620 23625 23630  
 Met Leu Glu Tyr Pro Asp Tyr Glu Leu Asp Glu Arg Tyr Gln Glu Gly  
 23635 23640 23645  
 Ile Phe Val Arg Gln Gly Gly Val Ile Arg Leu Thr Ile Pro Ile Lys  
 23650 23655 23660 2  
 Gly Lys Pro Phe Pro Ile Cys Lys Trp Thr Lys Glu Gly Gln Asp Ile  
 3665 23670 23675 23680  
 Ser Lys Arg Ala Met Ile Ala Thr Ser Glu Thr His Thr Glu Leu Val  
 23685 23690 23695  
 Ile Lys Glu Ala Asp Arg Gly Asp Ser Gly Thr Tyr Asp Leu Val Leu  
 23700 23705 23710  
 Glu Asn Lys Cys Gly Lys Lys Ala Val Tyr Ile Lys Val Arg Val Ile  
 23715 23720 23725  
 Gly Ser Pro Asn Ser Pro Glu Gly Pro Leu Glu Tyr Asp Asp Ile Gln  
 23730 23735 23740 2  
 Val Arg Ser Val Arg Val Ser Trp Arg Pro Pro Ala Asp Asp Gly Gly  
 3745 23750 23755 23760  
 Ala Asp Ile Leu Gly Tyr Ile Leu Glu Arg Arg Glu Val Pro Lys Ala  
 23765 23770 23775  
 Ala Trp Tyr Thr Ile Asp Ser Arg Val Arg Gly Thr Ser Leu Val Val  
 23780 23785 23790  
 Lys Gly Leu Lys Glu Asn Val Glu Tyr His Phe Arg Val Ser Ala Glu  
 23795 23800 23805  
 Asn Gln Phe Gly Ile Ser Lys Pro Leu Lys Ser Glu Glu Pro Val Thr  
 23810 23815 23820 2  
 Pro Lys Thr Pro Leu Asn Pro Pro Glu Pro Pro Ser Asn Pro Pro Glu  
 3825 23830 23835 23840  
 Val Leu Asp Val Thr Lys Ser Ser Val Ser Leu Ser Trp Ser Arg Pro  
 23845 23850 23855  
 Lys Asp Asp Gly Gly Ser Arg Val Thr Gly Tyr Tyr Ile Glu Arg Lys  
 23860 23865 23870  
 Glu Thr Ser Thr Asp Lys Trp Val Arg His Asn Lys Thr Gln Ile Thr  
 23875 23880 23885  
 Thr Thr Met Tyr Thr Val Thr Gly Leu Val Pro Asp Ala Glu Tyr Gln  
 23890 23895 23900 2  
 Phe Arg Ile Ile Ala Gln Asn Asp Val Gly Leu Ser Glu Thr Ser Pro  
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 Ala Ser Glu Pro Val Val Cys Lys Asp Pro Phe Asp Lys Pro Ser Gln  
 23925 23930 23935  
 Pro Gly Glu Leu Glu Ile Leu Ser Ile Ser Lys Asp Ser Val Thr Leu  
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 Gln Trp Glu Lys Pro Glu Cys Asp Gly Gly Lys Glu Ile Leu Gly Tyr  
 23955 23960 23965  
 Trp Val Glu Tyr Arg Gln Ser Gly Asp Ser Ala Trp Lys Lys Ser Asn  
 23970 23975 23980 2  
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 Ala Thr Glu Tyr Glu Phe Arg Val Phe Ala Glu Asn Glu Thr Gly Leu  
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 Ser Arg Pro Arg Arg Thr Ala Met Ser Ile Lys Thr Lys Leu Thr Ser  
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Gly Glu Ala Pro Gly Ile Arg Lys Glu Met Lys Asp Val Thr Thr Lys  
 24035 24040 24045  
 Leu Gly Glu Ala Ala Gln Leu Ser Cys Gln Ile Val Gly Arg Pro Leu  
 24050 24055 24060 2  
 Pro Asp Ile Lys Trp Tyr Arg Phe Gly Lys Glu Leu Ile Gln Ser Arg  
 4065 24070 24075 24080  
 Lys Tyr Lys Met Ser Ser Asp Gly Arg Thr His Thr Leu Thr Val Met  
 24085 24090 24095  
 Thr Glu Glu Gln Glu Asp Glu Gly Val Tyr Thr Cys Ile Ala Thr Asn  
 24100 24105 24110  
 Glu Val Gly Glu Val Glu Thr Ser Ser Lys Leu Leu Leu Gln Ala Thr  
 24115 24120 24125  
 Pro Gln Phe His Pro Gly Tyr Pro Leu Lys Glu Lys Tyr Tyr Gly Ala  
 24130 24135 24140 2  
 Val Gly Ser Thr Leu Arg Leu His Val Met Tyr Ile Gly Arg Pro Val  
 4145 24150 24155 24160  
 Pro Ala Met Thr Trp Phe His Gly Gln Lys Leu Leu Gln Asn Ser Glu  
 24165 24170 24175  
 Asn Ile Thr Ile Glu Asn Thr Glu His Tyr Thr His Leu Val Met Lys  
 24180 24185 24190  
 Asn Val Gln Arg Lys Thr His Ala Gly Lys Tyr Lys Val Gln Leu Ser  
 24195 24200 24205  
 Asn Val Phe Gly Thr Val Asp Ala Ile Leu Asp Val Glu Ile Gln Asp  
 24210 24215 24220 2  
 Lys Pro Asp Lys Pro Thr Gly Pro Ile Val Ile Glu Ala Leu Leu Lys  
 4225 24230 24235 24240  
 Asn Ser Ala Val Ile Ser Trp Lys Pro Pro Ala Asp Asp Gly Gly Ser  
 24245 24250 24255  
 Trp Ile Thr Asn Tyr Val Val Glu Lys Cys Glu Ala Lys Glu Gly Ala  
 24260 24265 24270  
 Glu Trp Gln Leu Val Ser Ser Ala Ile Ser Val Thr Thr Cys Arg Ile  
 24275 24280 24285  
 Val Asn Leu Thr Glu Asn Ala Gly Tyr Tyr Phe Arg Val Ser Ala Gln  
 24290 24295 24300 2  
 Asn Thr Phe Gly Ile Ser Asp Pro Leu Glu Val Ser Ser Val Val Ile  
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 Ile Lys Ser Pro Phe Glu Lys Pro Gly Ala Pro Gly Lys Pro Thr Ile  
 24325 24330 24335  
 Thr Ala Val Thr Lys Asp Ser Cys Val Val Ala Trp Lys Pro Pro Ala  
 24340 24345 24350  
 Ser Asp Gly Gly Ala Lys Ile Arg Asn Tyr Tyr Leu Glu Lys Arg Glu  
 24355 24360 24365  
 Lys Lys Gln Asn Lys Trp Ile Ser Val Thr Thr Glu Glu Ile Arg Glu  
 24370 24375 24380 2  
 Thr Val Phe Ser Val Lys Asn Leu Ile Glu Gly Leu Glu Tyr Glu Phe  
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 Arg Val Lys Cys Glu Asn Leu Gly Gly Glu Ser Glu Trp Ser Glu Ile  
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 Ser Glu Pro Ile Thr Pro Lys Ser Asp Val Pro Ile Gln Ala Pro His  
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 Phe Lys Glu Glu Leu Arg Asn Leu Asn Val Arg Tyr Gln Ser Asn Ala  
 24435 24440 24445  
 Thr Leu Val Cys Lys Val Thr Gly His Pro Lys Pro Ile Val Lys Trp  
 24450 24455 24460 2  
 Tyr Arg Gln Gly Lys Glu Ile Ile Ala Asp Gly Leu Lys Tyr Arg Ile  
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 Gln Glu Phe Lys Gly Gly Tyr His Gln Leu Ile Ile Ala Ser Val Thr  
 24485 24490 24495  
 Asp Asp Asp Ala Thr Val Tyr Gln Val Arg Ala Thr Asn Gln Gly Gly  
 24500 24505 24510  
 Ser Val Ser Gly Thr Ala Ser Leu Glu Val Glu Val Pro Ala Lys Ile  
 24515 24520 24525

His Leu Pro Lys Thr Leu Glu Gly Met Gly Ala Val His Ala Leu Arg  
 24530 24535 24540 2  
 Gly Glu Val Val Ser Ile Lys Ile Pro Phe Ser Gly Lys Pro Asp Pro  
 4545 24550 24555 24560  
 Val Ile Thr Trp Gln Lys Gly Gln Asp Leu Ile Asp Asn Asn Gly His  
 24565 24570 24575  
 Tyr Gln Val Ile Val Thr Arg Ser Phe Thr Ser Leu Val Phe Pro Asn  
 24580 24585 24590  
 Gly Val Glu Arg Lys Asp Ala Gly Phe Tyr Val Val Cys Ala Lys Asn  
 24595 24600 24605  
 Arg Phe Gly Ile Asp Gln Lys Thr Val Glu Leu Asp Val Ala Asp Val  
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 Pro Asp Pro Pro Arg Gly Val Lys Val Ser Asp Ala Ser Arg Asp Ser  
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 Val Asn Leu Thr Trp Thr Glu Pro Ala Ser Asp Gly Gly Ser Lys Ile  
 24645 24650 24655  
 Thr Asn Tyr Ile Val Glu Lys Cys Ala Thr Thr Ala Glu Arg Trp Leu  
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 Arg Val Gly Gln Ala Arg Glu Thr Arg Tyr Thr Val Ile Asn Leu Phe  
 24675 24680 24685  
 Gly Lys Thr Ser Tyr Gln Phe Arg Val Ile Ala Glu Asn Lys Phe Gly  
 24690 24695 24700 2  
 Leu Ser Lys Pro Ser Glu Pro Ser Glu Pro Thr Ile Thr Lys Glu Asp  
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 Lys Thr Arg Ala Met Asn Tyr Asp Glu Glu Val Asp Glu Thr Arg Glu  
 24725 24730 24735  
 Val Ser Met Thr Lys Ala Ser His Ser Ser Thr Lys Glu Leu Tyr Glu  
 24740 24745 24750  
 Lys Tyr Met Ile Ala Glu Asp Leu Gly Arg Gly Glu Phe Gly Ile Val  
 24755 24760 24765  
 His Arg Cys Val Glu Thr Ser Ser Lys Lys Thr Tyr Met Ala Lys Phe  
 24770 24775 24780 2  
 Val Lys Val Lys Gly Thr Asp Gln Val Leu Val Lys Lys Glu Ile Ser  
 4785 24790 24795 24800  
 Ile Leu Asn Ile Ala Arg His Arg Asn Ile Leu His Leu His Glu Ser  
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 Leu Asp Ile Phe Glu Arg Ile Asn Thr Ser Ala Phe Glu Leu Asn Glu  
 24835 24840 24845  
 Arg Glu Ile Val Ser Tyr Val His Gln Val Cys Glu Ala Leu Gln Phe  
 24850 24855 24860 2  
 Leu His Ser His Asn Ile Gly His Phe Asp Ile Arg Pro Glu Asn Ile  
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 Ile Tyr Gln Thr Arg Arg Ser Ser Thr Ile Lys Ile Ile Glu Phe Gly  
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 Gln Ala Arg Gln Leu Lys Pro Gly Asp Asn Phe Arg Leu Leu Phe Thr  
 24900 24905 24910  
 Ala Pro Glu Tyr Tyr Ala Pro Glu Val His Gln His Asp Val Val Ser  
 24915 24920 24925  
 Thr Ala Thr Asp Met Trp Ser Leu Gly Thr Leu Val Tyr Val Leu Leu  
 24930 24935 24940 2  
 Ser Gly Ile Asn Pro Phe Leu Ala Glu Thr Asn Gln Gln Ile Ile Glu  
 4945 24950 24955 24960  
 Asn Ile Met Asn Ala Glu Tyr Thr Phe Asp Glu Glu Ala Phe Lys Glu  
 24965 24970 24975  
 Ile Ser Ile Glu Ala Met Asp Phe Val Asp Arg Leu Leu Val Lys Glu  
 24980 24985 24990  
 Arg Lys Ser Arg Met Thr Ala Ser Glu Ala Leu Gln His Pro Trp Leu  
 24995 25000 25005  
 Lys Gln Lys Ile Glu Arg Val Ser Thr Lys Val Ile Arg Thr Leu Lys  
 25010 25015 25020 2

His Arg Arg Tyr Tyr His Thr Leu Ile Lys Lys Asp Leu Asn Met Val  
 5025 25030 25035 25040  
 Val Ser Ala Ala Arg Ile Ser Cys Gly Gly Ala Ile Arg Ser Gln Lys  
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 Gly Val Ser Val Ala Lys Val Lys Val Ala Ser Ile Glu Ile Gly Pro  
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 Val Ser Gly Gln Ile Met His Ala Val Gly Glu Glu Gly Gly His Val  
 25075 25080 25085  
 Lys Tyr Val Cys Lys Ile Glu Asn Tyr Asp Gln Ser Thr Gln Val Thr  
 25090 25095 25100 2  
 Trp Tyr Phe Gly Val Arg Gln Leu Glu Asn Ser Glu Lys Tyr Glu Ile  
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 Thr Tyr Glu Asp Gly Val Ala Ile Leu Tyr Val Lys Asp Ile Thr Lys  
 25125 25130 25135  
 Leu Asp Asp Gly Thr Tyr Arg Cys Lys Val Val Asn Asp Tyr Gly Glu  
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 Asp Ser Ser Tyr Ala Glu Leu Phe Val Lys Gly Val Arg Glu Val Tyr  
 25155 25160 25165  
 Asp Tyr Tyr Cys Arg Arg Thr Met Lys Lys Ile Lys Arg Arg Thr Asp  
 25170 25175 25180 2  
 Thr Met Arg Leu Leu Glu Arg Pro Pro Glu Phe Thr Leu Pro Leu Tyr  
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 Asn Lys Thr Ala Tyr Val Gly Glu Asn Val Arg Phe Gly Val Thr Ile  
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 Thr Val His Pro Glu Pro His Val Thr Trp Tyr Lys Ser Gly Gln Lys  
 25220 25225 25230  
 Ile Lys Pro Gly Asp Asn Asp Lys Lys Tyr Thr Phe Glu Ser Asp Lys  
 25235 25240 25245  
 Gly Leu Tyr Gln Leu Thr Ile Asn Ser Val Thr Thr Asp Asp Ala  
 25250 25255 25260 2  
 Glu Tyr Thr Val Val Ala Arg Asn Lys Tyr Gly Glu Asp Ser Cys Lys  
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 Ala Lys Leu Thr Val Thr Leu His Pro Pro Pro Thr Asp Ser Thr Leu  
 25285 25290 25295  
 Arg Pro Met Phe Lys Arg Leu Leu Ala Asn Ala Glu Cys Gln Glu Gly  
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 Gln Ser Val Cys Phe Glu Ile Arg Val Ser Gly Ile Pro Pro Pro Thr  
 25315 25320 25325  
 Leu Lys Trp Glu Lys Asp Gly Gln Pro Leu Ser Leu Gly Pro Asn Ile  
 25330 25335 25340 2  
 Glu Ile Ile His Glu Gly Leu Asp Tyr Tyr Ala Leu His Ile Arg Asp  
 5345 25350 25355 25360  
 Thr Leu Pro Glu Asp Thr Gly Tyr Tyr Arg Val Thr Ala Thr Asn Thr  
 25365 25370 25375  
 Ala Gly Ser Thr Ser Cys Gln Ala His Leu Gln Val Glu Arg Leu Arg  
 25380 25385 25390  
 Tyr Lys Lys Gln Glu Phe Lys Ser Lys Glu Glu His Glu Arg His Val  
 25395 25400 25405  
 Gln Lys Gln Ile Asp Lys Thr Leu Arg Met Ala Glu Ile Leu Ser Gly  
 25410 25415 25420 2  
 Thr Glu Ser Val Pro Leu Thr Gln Val Ala Lys Glu Ala Leu Arg Glu  
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 Ala Ala Val Leu Tyr Lys Pro Ala Val Ser Thr Lys Thr Val Lys Gly  
 25445 25450 25455  
 Glu Phe Arg Leu Glu Ile Glu Glu Lys Lys Glu Glu Arg Lys Leu Arg  
 25460 25465 25470  
 Met Pro Tyr Asp Val Pro Glu Pro Arg Lys Tyr Lys Gln Thr Thr Ile  
 25475 25480 25485  
 Glu Glu Asp Gln Arg Ile Lys Gln Phe Val Pro Met Ser Asp Met Lys  
 25490 25495 25500 2  
 Trp Tyr Lys Lys Ile Arg Asp Gln Tyr Glu Met Pro Gly Lys Leu Asp  
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Arg Val Val Gln Lys Arg Pro Lys Arg Ile Arg Leu Ser Arg Trp Glu  
 25525 25530 25535  
 Gln Phe Tyr Val Met Pro Leu Pro Arg Ile Thr Asp Gln Tyr Arg Pro  
 25540 25545 25550  
 Lys Trp Arg Ile Pro Lys Leu Ser Gln Asp Asp Leu Glu Ile Val Arg  
 25555 25560 25565  
 Pro Ala Arg Arg Arg Thr Pro Ser Pro Asp Tyr Asp Phe Tyr Tyr Arg  
 25570 25575 25580 2  
 Pro Arg Arg Arg Ser Leu Gly Asp Ile Ser Asp Glu Glu Leu Leu Leu  
 5585 25590 25595 25600  
 Pro Ile Asp Asp Tyr Leu Ala Met Lys Arg Thr Glu Glu Glu Arg Leu  
 25605 25610 25615  
 Arg Leu Glu Glu Glu Leu Glu Leu Gly Phe Ser Ala Ser Pro Pro Ser  
 25620 25625 25630  
 Arg Ser Pro Pro His Phe Glu Leu Ser Ser Leu Arg Tyr Ser Ser Pro  
 25635 25640 25645  
 Gln Ala His Val Lys Val Glu Glu Thr Arg Lys Asn Phe Arg Tyr Ser  
 25650 25655 25660 2  
 Thr Tyr His Ile Pro Thr Lys Ala Glu Ala Ser Thr Ser Tyr Ala Glu  
 5665 25670 25675 25680  
 Leu Arg Glu Arg His Ala Gln Ala Ala Tyr Arg Gln Pro Lys Gln Arg  
 25685 25690 25695  
 Gln Arg Ile Met Ala Glu Arg Glu Asp Glu Glu Leu Leu Arg Pro Val  
 25700 25705 25710  
 Thr Thr Thr Gln His Leu Ser Glu Tyr Lys Ser Glu Leu Asp Phe Met  
 25715 25720 25725  
 Ser Lys Glu Glu Lys Ser Arg Lys Lys Ser Arg Arg Gln Arg Glu Val  
 25730 25735 25740 2  
 Thr Glu Ile Thr Glu Ile Glu Glu Glu Tyr Glu Ile Ser Lys His Ala  
 5745 25750 25755 25760  
 Gln Arg Glu Ser Ser Ser Ser Ala Ser Arg Leu Leu Arg Arg Arg Arg  
 25765 25770 25775  
 Ser Leu Ser Pro Thr Tyr Ile Glu Leu Met Arg Pro Val Ser Glu Leu  
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US01/01212

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C12Q 1/68; A61K 48/00; C12N 15/00

US CL : 435/6; 514/44; 800/21

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 514/44; 800/21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, caplus, medline, uspatful

search terms: titin gene, mutation, pickwick, heart disease, cardiac, cardio?, zebrafish

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- A	SATOH. M. Structural Analysis of the Titin Gene in Hypertrophic Cardiomyopathy: Identification of a Novel Disease Gene. Biochemical and Biophysical Research Communications. August 1999. Vol 262. pages 411-417, especially abstract, page 412, Fig.3, page 414.	1-6 ----- 7-19
A	SIU. B.L. Familial Dilated Cardiomyopathy Locus Maps to Chromosome 2q31. Circulation. 02 March 1999. Vol 99. pages 1022-1026, especially abstract, Fig. 3.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 FEBRUARY 2001

Date of mailing of the international search report

16 MAY 2001

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JEHANNE SOUAYA

Telephone No. (703) 308-1235

**TERRY J. DEY**  
**PARALEGAL SPECIALIST**  
**TECHNOLOGY CENTER 1600**